

OHSU Authors Bibliography

June 2017 – 262 Articles

Abadia, A. F., Grant, K. L., Carey, K. E., Bolch, W. E., & Morin, R. L. (2017). **Spatial Distribution of Iron Within the Normal Human Liver Using Dual-Source Dual-Energy CT Imaging.** *Investigative Radiology*. doi:10.1097/RLI.0000000000000393

OBJECTIVES: Explore the potential of dual-source dual-energy (DSDE) computed tomography (CT) to retrospectively analyze the uniformity of iron distribution and establish iron concentration ranges and distribution patterns found in healthy livers. **MATERIALS AND METHODS:** Ten mixtures consisting of an iron nitrate solution and deionized water were prepared in test tubes and scanned using a DSDE 128-slice CT system. Iron images were derived from a 3-material decomposition algorithm (optimized for the quantification of iron). A conversion factor (mg Fe/mL per Hounsfield unit) was calculated from this phantom study as the quotient of known tube concentrations and their corresponding CT values. Retrospective analysis was performed of patients who had undergone DSDE imaging for renal stones. Thirty-seven patients with normal liver function were randomly selected (mean age, 52.5 years). The examinations were processed for iron concentration. Multiple regions of interest were analyzed, and iron concentration (mg Fe/mL) and distribution was reported. **RESULTS:** The mean conversion factor obtained from the phantom study was 0.15 mg Fe/mL per Hounsfield unit. Whole-liver mean iron concentrations yielded a range of 0.0 to 2.91 mg Fe/mL, with 94.6% (35/37) of the patients exhibiting mean concentrations below 1.0 mg Fe/mL. The most important finding was that iron concentration was not uniform and patients exhibited regionally high concentrations (36/37). These regions of higher concentration were observed to be dominant in the middle-to-upper part of the liver (75%), medially (72.2%), and anteriorly (83.3%). **CONCLUSIONS:** Dual-source dual-energy CT can be used to assess the uniformity of iron distribution in healthy subjects. Applying similar techniques to unhealthy livers, future research may focus on the impact of hepatic iron content and distribution for noninvasive assessment in diseased subjects. Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

Ahn, J., Lim, J. K., Lee, H. M., Lok, A. S., Nguyen, M., Pan, C. Q., . . . Kim, W. R. (2016). **Lower Observed Hepatocellular Carcinoma Incidence in Chronic Hepatitis B Patients Treated With Entecavir: Results of the ENUMERATE Study.** *Am J Gastroenterol*, 111(9), 1297-1304. doi:10.1038/ajg.2016.257

OBJECTIVES: Data from the United States are lacking regarding the impact of entecavir (ETV) on the risk of hepatocellular carcinoma (HCC). Our aim is to determine whether treatment with ETV is associated with a reduced HCC risk by calculating the expected HCC incidence based on the Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B (REACH-B) model and comparing it with the observed HCC incidence. **METHODS:** The incidence of HCC in US patients treated with ETV between 2005 and 2013 in a retrospective cohort was obtained. The predicted HCC incidence was calculated using the REACH-B model. The standardized incidence ratios (SIRs) were calculated as a ratio of observed over predicted HCC cases. **RESULTS:** Of 841 patients, 646 (65% male, 84% Asian, median age 47 years, 36% hepatitis B e antigen positive, 9.4% with cirrhosis) met the inclusion criteria. Over a median follow-up of 4 years, 17 (2.6%) cases of HCC were diagnosed, including 8 out of 61 (13.1%) patients with cirrhosis and 9 out of 585 (1.5%) without cirrhosis. Compared with those without HCC, the 17 patients with HCC were older at 53 years vs. 47 years and more likely to have cirrhosis at 47.1% vs. 8.4%. Among patients without cirrhosis, the observed HCC incidence was significantly lower than predicted by the fourth year (SIR, 0.37; 95% confidence interval: 0.166-0.82). A sensitivity analysis that comprised all patients, including those with cirrhosis, showed that at the maximum follow-up time of 8.2 years, a significantly lower than predicted HCC incidence was noted with an SIR of 0.56 (95% confidence interval: 0.35-0.905). **CONCLUSIONS:** Based on the REACH-B model, long-term ETV therapy was associated with a lower than predicted HCC incidence. However, the risk of HCC persisted, and careful HCC surveillance remains warranted despite the anti-viral treatment.

Allen, A. S., Berkovic, S. F., Bridgers, J., Cossette, P., Dlugos, D., Epstein, M. P., . . . Winawer, M. R. (2017). **Application of rare variant transmission disequilibrium tests to epileptic encephalopathy trio sequence data.** *European Journal of Human Genetics*, 25(7), 894-899. doi:10.1038/ejhg.2017.61

The classic epileptic encephalopathies, including infantile spasms (IS) and Lennox-Gastaut syndrome (LGS), are severe seizure disorders that usually arise sporadically. De novo variants in genes mainly encoding ion channel and synaptic proteins have been found to account for over 15% of patients with IS or LGS. The contribution of autosomal recessive genetic variation, however, is less well understood. We implemented a rare variant transmission disequilibrium test (TDT) to search for autosomal recessive epileptic encephalopathy genes in a cohort of 320 outbred patient-parent trios that were generally prescreened for rare metabolic disorders. In the current sample, our rare variant transmission disequilibrium test did not identify individual genes with significantly distorted transmission over expectation after correcting for the multiple tests. While the rare variant transmission disequilibrium test did not find evidence of a role for individual autosomal recessive genes, our current sample is insufficiently powered to assess the overall role of autosomal recessive genotypes in an outbred epileptic encephalopathy population. © 2017 Macmillan Publishers Limited, part of Springer Nature. All rights reserved.

Al-Uzri, A., Freeman, K. A., Wade, J., Clark, K., Bleyl, L. A., Munar, M., & Koop, D. R. (2017). **Longitudinal study on the use of dried blood spots for home monitoring in children after kidney transplantation.** *Pediatric Transplantation*. doi:10.1111/ptr.12983

The use of DBSs for home monitoring has been limited due to unsatisfactory blood sampling and analytical difficulties. The aim of this longitudinal feasibility trial was to assess the utility of DBS to monitor TAC and Cr at home in transplant recipients. A total of 30 participants (2-21 years, mean \pm SD, 13.6 \pm 5.4 year) were enrolled over 12 months. Eighteen were males. Monthly DBS samples were obtained at home and mailed to the central laboratory for analysis of TAC and Cr. Nineteen patients completed the study, and 216 cards were received in the laboratory from a total of 279 cards expected, with 416/519 (80%) blood spots being suitable for analysis. We found a high correlation between blood TAC and Cr levels by DBS and the clinical laboratory, $R^2 = .81$ and $.95$, respectively. Fifteen parents and 15 youth completed measures of satisfaction with and preference for DBS testing. All but one parent/caregiver and youth reported satisfaction and preference for this method of testing over laboratory blood draws. We conclude that home DBS monitoring is a feasible method to monitor TAC and Cr in pediatric transplant recipients.

Ambady, P., Fu, R., Netto, J. P., Kersch, C., Firkins, J., Doolittle, N. D., & Neuwelt, E. A. (2017). **Patterns of relapse in primary central nervous system lymphoma: Inferences regarding the role of the neuro-vascular unit and monoclonal antibodies in treating occult CNS disease.** *Fluids Barriers CNS*, 14(1). doi:10.1186/s12987-017-0064-3

Background and purpose: The radiologic features and patterns of primary central nervous system lymphoma (PCNSL) at initial presentation are well described. High response rates can be achieved with first-line high-dose methotrexate (HD-MTX) based regimens, yet many relapse within 2 years of diagnosis. We describe the pattern of relapse and review the potential mechanisms involved in relapse. **Methods:** We identified 78 consecutive patients who attained complete radiographic response (CR) during or after first-line treatment for newly diagnosed PCNSL (CD20+, diffuse large B cell type). Patients were treated with HD-MTX based regimen in conjunction with blood-brain barrier disruption (HD-MTX/BBBD); 44 subsequently relapsed. Images and medical records of these 44 consecutive patients were retrospectively reviewed. The anatomical location of enhancing lesions at initial diagnosis and at the time of relapse were identified and compared. **Results:** 37/44 patients fulfilled inclusion criteria and had new measurable enhancing lesions at relapse; the pattern and location of relapse of these 37 patients were identified. At relapse, the new enhancement was at a spatially distinct site in 30 of 37 patients. Local relapse was found only in seven patients. **Discussion:** Unlike gliomas, the majority of PCNSL had radiographic relapse at spatially distinct anatomical locations within the brain behind a previously intact neurovascular unit (NVU), and in few cases outside, the central nervous

system (CNS). This may suggest either (1) reactivation of occult reservoirs behind an intact NVU in the CNS (or ocular) or (2) seeding from bone marrow or other extra CNS sites. Conclusion: Recognizing patterns of relapse is key for early detection and may provide insight into potential mechanisms of relapse as well as help develop strategies to extend duration of complete response. © 2017 The Author(s).

Anderson, D. E., Rose, M. B., Wille, A. J., Wiedrick, J., & Crawford, D. C. (2017). **Arthroscopic mechanical chondroplasty of the knee is beneficial for treatment of focal cartilage lesions in the absence of concurrent pathology.** *Orthopaedic Journal of Sports Medicine*, 5(5). doi:10.1177/2325967117707213

Background: Articular cartilage lacks the ability for intrinsic repair after acute injury, and focal articular cartilage lesions cause significant morbidity worldwide. Arthroscopic debridement (chondroplasty) represents the majority of cartilage procedures of the knee; however, limited data exist regarding outcomes after chondroplasty performed in isolation of concurrent procedures or not as a primary treatment for osteoarthritis (OA). Hypothesis: Arthroscopic mechanical chondroplasty is beneficial for patients with a focal cartilage lesion of the knee in the absence of meniscal pathology or OA. Study Design: Case series; Level of evidence, 4. Methods: Potential participants were identified by querying billing data from a 3-year period in a single-surgeon practice, and eligible patients were verified to meet inclusion criteria through electronic medical record review. OA was quantified through Kellgren-Lawrence (KL) scoring. Subjective patient-reported outcome (PRO) scores, including International Knee Documentation Committee (IKDC), Knee injury and Osteoarthritis Outcome Score (KOOS), Western Ontario and McMaster Universities Arthritis Index (WOMAC), Tegner, Lysholm, and Veterans RAND 12-Item Health Survey (VR-12), were collected preoperatively and at follow-up intervals. International Cartilage Repair Society (ICRS) grade and lesion size were determined at arthroscopy. Linear regression was used to determine the effect of baseline score on final follow-up score. Correlated regression equations were used to assess the relationship of covariates and change in PRO scores. Results: Fifty-three of 86 (62%) eligible participants completed postoperative questionnaires at an average of 31.5 months (range, 11.5-57 months). The mean patient age was 37.3 ± 9.7 years and mean body mass index (BMI) was 27.7 ± 5.6 kg/m²; 33 (62%) participants were women. The mean treated lesion size was 3.3 ± 1.9 cm², of these, 36 (68%) were ICRS grade 2 or 3, and 42 (79%) patients had a KL score of 0 to -2. On average, the cohort demonstrated significant improvement from baseline for almost all PRO scores. Regression analysis of change in score versus baseline indicated participants with lower preoperative scores gained more benefit from chondroplasty. Correlated regression equations showed KL score ≥ 0 and male sex had a consistent positive effect on change in PRO scores, high ICRS grade had a consistent negative effect, and lesion size, age, and obesity had no effect. Eight patients (15%) required further surgical intervention within the follow-up period. Conclusion: The clinical efficacy of chondroplasty for repair of focal cartilage defects of the knee has not been studied in isolation from concurrent orthopaedic procedures. Our data show that arthroscopic mechanical chondroplasty is beneficial to patients, and response to surgical intervention is correlated with baseline PRO scores, sex, ICRS grade, and KL score. © The Author(s) 2017.

Anney, R. J. L., Ripke, S., Anttila, V., Grove, J., Holmans, P., Huang, H., . . . Hakonarson, H. (2017). **Meta-analysis of GWAS of over 16,000 individuals with autism spectrum disorder highlights a novel locus at 10q24.32 and a significant overlap with schizophrenia.** *Molecular Autism*, 8(1). doi:10.1186/s13229-017-0137-9

Background: Over the past decade genome-wide association studies (GWAS) have been applied to aid in the understanding of the biology of traits. The success of this approach is governed by the underlying effect sizes carried by the true risk variants and the corresponding statistical power to observe such effects given the study design and sample size under investigation. Previous ASD GWAS have identified genome-wide significant (GWS) risk loci; however, these studies were of only of low statistical power to identify GWS loci at the lower effect sizes (odds ratio (OR) ≤ 1.15). Methods: We conducted a large-scale coordinated international collaboration to combine independent genotyping data to improve the statistical power and aid in robust discovery of GWS loci. This study uses genome-wide genotyping data from a discovery sample (7387 ASD cases and 8567 controls) followed by meta-analysis of summary statistics from two replication sets (7783 ASD cases and 11359 controls; and 1369 ASD cases and 137308 controls). Results: We observe a

GWS locus at 10q24.32 that overlaps several genes including PITX3, which encodes a transcription factor identified as playing a role in neuronal differentiation and CUEDC2 previously reported to be associated with social skills in an independent population cohort. We also observe overlap with regions previously implicated in schizophrenia which was further supported by a strong genetic correlation between these disorders ($R_g = 0.23$; $P = 9 \times 10^{-6}$). We further combined these Psychiatric Genomics Consortium (PGC) ASD GWAS data with the recent PGC schizophrenia GWAS to identify additional regions which may be important in a common neurodevelopmental phenotype and identified 12 novel GWS loci. These include loci previously implicated in ASD such as FOXP1 at 3p13, ATP2B2 at 3p25.3, and a 'neurodevelopmental hub' on chromosome 8p11.23. Conclusions: This study is an important step in the ongoing endeavour to identify the loci which underpin the common variant signal in ASD. In addition to novel GWS loci, we have identified a significant genetic correlation with schizophrenia and association of ASD with several neurodevelopmental-related genes such as EXT1, ASTN2, MACROD2, and HDAC4. © 2017 The Author(s).

Api, A. M., Belsito, D., Bhatia, S., Botelho, D., Browne, D., Bruze, M., . . . Wilcox, D. K. (2017). **RIFM fragrance ingredient safety assessment, dihydro- α -terpineol, CAS Registry Number 498-81-7.** *Food and Chemical Toxicology*. doi:10.1016/j.fct.2017.05.063

Api, A. M., Belsito, D., Bhatia, S., Botelho, D., Browne, D., Bruze, M., . . . Wilcox, D. K. (2016). **RIFM fragrance ingredient safety assessment, 4-(3,4-methylenedioxyphenyl)-2-butanone, CAS Registry Number 55418-52-5.** *Food and Chemical Toxicology*. doi:10.1016/j.fct.2017.06.008

Api, A. M., Belsito, D., Bhatia, S., Botelho, D., Browne, D., Bruze, M., . . . Wilcox, D. K. (2017). **RIFM fragrance ingredient safety assessment, Methyl hexyl oxo cyclopentanone carboxylate, CAS Registry Number 37172-53-5.** *Food Chem Toxicol*. doi:10.1016/j.fct.2017.06.028

Api, A. M., Belsito, D., Botelho, D., Browne, D., Bruze, M., Burton, G. A., . . . Wahler, J. (2017). **RIFM fragrance ingredient safety assessment, α -methylcyclohexylmethyl acetate, CAS Registry Number 13487-27-9.** *Food and Chemical Toxicology*. doi:10.1016/j.fct.2017.05.064

Api, A. M., Belsito, D., Botelho, D., Browne, D., Bruze, M., Burton, G. A., . . . Wahler, J. (2017). **RIFM fragrance ingredient safety assessment, acetic acid, C7-9-branched alkyl esters, C8-rich, CAS Registry Number 108419-32-5.** *Food and Chemical Toxicology*. doi:10.1016/j.fct.2017.05.066

The use of this material under current conditions is supported by existing information. This material was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data show that this material is not genotoxic. Data from the suitable read across analog isoamyl acetate (CAS# 123-92-2) show that this material does not have skin sensitization potential. The reproductive and local respiratory toxicity endpoints were completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (0.03 mg/kg/day and 1.4 mg/day, respectively). The repeated dose and developmental endpoint was completed using data on the target material, which provided a MOE > 100. The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra. The environmental endpoint was completed as described in the RIFM Framework. © 2017 Elsevier Ltd.

Api, A. M., Belsito, D., Botelho, D., Browne, D., Bruze, M., Burton, G. A., Jr., . . . Wahler, J. (2017). **RIFM fragrance ingredient safety assessment, benzenepropanenitrile, 4-ethyl-.alpha.,.alpha.-dimethyl, CAS Registry Number 134123-93-6.** *Food Chem Toxicol.* doi:10.1016/j.fct.2017.06.026

Api, A. M., Belsito, D., Botelho, D., Browne, D., Bruze, M., Burton, G. A., . . . Wahler, J. (2017). **RIFM fragrance ingredient safety assessment, benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester, CAS Registry Number 25628-84-6.** *Food and Chemical Toxicology.* doi:10.1016/j.fct.2017.06.002

Api, A. M., Belsito, D., Botelho, D., Browne, D., Bruze, M., Burton, G. A., Jr., . . . Wahler, J. (2017). **RIFM fragrance ingredient safety assessment, isodecyl alcohol, CAS registry number 25339-17-7.** *Food Chem Toxicol.* doi:10.1016/j.fct.2017.06.027

Api, A. M., Belsito, D., Botelho, D., Bruze, M., Calow, P., Dagli, M. L., . . . Wahler, J. (2017). **RIFM fragrance ingredient safety assessment, 2-tert-butylcyclohexanol, CAS Registry Number 13491-79-7.** *Food and Chemical Toxicology.* doi:10.1016/j.fct.2017.05.062

Artz, A. S., Logan, B., Zhu, X., Akpek, G., Bufarull, R. M., Gupta, V., . . . Cooke, K. R. (2016). **The prognostic value of serum C-reactive protein, ferritin, and albumin prior to allogeneic transplantation for acute myeloid leukemia and myelodysplastic syndromes.** *Haematologica*, 101(11), 1426-1433. doi:10.3324/haematol.2016.145847

We sought to confirm the prognostic importance of simple clinically available biomarkers of C-reactive protein, serum albumin, and ferritin prior to allogeneic hematopoietic cell transplantation. The study population consisted of 784 adults with acute myeloid leukemia in remission or myelodysplastic syndromes undergoing unrelated donor transplant reported to the Center for International Blood and Marrow Transplant Research. C-reactive protein and ferritin were centrally quantified by ELISA from cryopreserved plasma whereas each center provided pre-transplant albumin. In multivariate analysis, transplant-related mortality was associated with the pre-specified thresholds of C-reactive protein more than 10 mg/L (P=0.008) and albumin less than 3.5 g/dL (P=0.01) but not ferritin more than 2500 ng/mL. Only low albumin independently influenced overall mortality. Optimal thresholds affecting transplant-related mortality were defined as: C-reactive protein more than 3.67 mg/L, log(ferritin), and albumin less than 3.4 g/dL. A 3-level biomarker risk group based on these values separated risks of transplant-related mortality: low risk (reference), intermediate (HR=1.66, P=0.015), and high risk (HR=2.7, P<0.001). One-year survival was 74%, 67% and 56% for low-, intermediate- and high-risk groups. Routinely available pre-transplant biomarkers independently risk-stratify for transplant-related mortality and survival.

Asquith, M., Davin, S., Stauffer, P., Michell, C., Janowitz, C., Lin, P., . . . Rosenbaum, J. (2017). **Intestinal metabolites are profoundly altered in the context of HLA-B27 expression and functionally modulate disease in a rat model of spondyloarthritis.** *Arthritis Rheumatol.* doi:10.1002/art.40183

Objective HLA-B27 associated spondyloarthropathies are associated with an altered intestinal microbiota and bowel inflammation. Therefore, we sought to identify B27-dependent changes in both host and microbial metabolites in the HLA-B27/beta2m rat and whether microbiota-derived metabolites could impact disease in this major model of spondyloarthritis. Methods Cecal contents were collected from 6wk (pre-diseased) and 16wk (diseased) Fischer 344 HLA-B27/beta2m transgenic rats and WT controls. Metabolomic profiling

was performed by high-throughput gas- and liquid-chromatography-based mass spectrometry. HLA-B27/beta2m rats were treated with microbial metabolites propionate or butyrate in drinking water for 10wks and disease activity subsequently assessed. Results Our screen identified 582 metabolites, of which over half were significantly altered by B27 expression at 16wks. Both microbial and host metabolites were altered, with multiple pathways including amino acid, carbohydrate, xenobiotic and medium chain fatty acid metabolism affected. Differences were even observed at 6wks, with upregulation of histidine, tyrosine, spermidine, N-acetylmuramate and glycerate in HLA-B27/beta2m rats. Administration of the short chain fatty acid propionate significantly attenuated B27-associated inflammatory disease, albeit was not associated with increased FoxP3+ T cell induction, or altered expression of cytokines IL-10, IL-33 or tight junction protein ZO-1. HLA-B27 expression was also associated with altered host expression of microbial metabolite receptor genes FFAR2, FFAR3 and NIACR1. Conclusion HLA-B27 expression profoundly impacts the intestinal metabolome, with changes evident in rats even at 6wks of age. Critically, we demonstrate a microbial metabolite, propionate attenuates development of B27-associated inflammatory disease. These and other microbiota-derived bioactive mediators may provide novel treatment modalities in B27-associated spondyloarthropathies. This article is protected by copyright. All rights reserved.

Asquith, M., & Rosenbaum, J. T. (2016). **The interaction between host genetics and the microbiome in the pathogenesis of spondyloarthropathies.** *Current Opinion in Rheumatology*, 28(4), 405-412.
doi:10.1097/bor.0000000000000299

PURPOSE OF REVIEW: The intestinal microbiome is increasingly implicated in the pathogenesis of ankylosing spondylitis, reactive arthritis, and other diseases collectively known as the spondyloarthropathies (SpAs). In common with other complex inflammatory diseases, SpAs have both a strong genetic and environmental component. Recent genetic studies have highlighted host pathways that may intersect the host-microbiota interaction and offer novel paradigms to understand the pathophysiology of these diseases. **RECENT FINDINGS:** Genetic association studies have identified genes such as RUNX3, PTPEN2, and IL-33 as susceptibility loci for SpAs. Functional studies in humans have extended knowledge of established genetic risk factors for ankylosing spondylitis that include ERAP1, ERAP2, and interleukin-23R. Recent basic research has identified new mechanisms that regulate host immune responses to the microbiota that conceivably may be dysregulated in SpA. **SUMMARY:** Intestinal barrier function, deletional tolerance, Th17 signature response, and endoplasmic reticulum stress pathways have been recently linked to SpA. Dysregulated immune responses to the gut microbiota and an altered microbial community structure are shared features of SpA. Although the cause-effect dynamic of this relationship remains equivocal, it nonetheless has major implications for both intestinal and extra-intestinal pathology observed in SpA.

Auerbach, M., & Deloughery, T. (2016). **Single-dose intravenous iron for iron deficiency: a new paradigm.** *Hematology: The Education Program of the American Society of Hematology*, 2016(1), 57-66.
doi:10.1182/asheducation-2016.1.57

Iron-deficiency anemia is the most common hematologic problem in the world. Although oral iron is often viewed as front-line therapy, extensive published evidence has accumulated that IV iron is superior, in both efficacy and safety, to oral iron in many clinical situations and should be introduced much sooner in the treatment paradigm of iron-deficient patients. In this chapter, we will review the formulations of IV iron that allow total complete replacement doses in 1 or 2 sessions including practical tips for administration. We realize safety concerns abound and therefore will analyze evidence based overstated concerns regarding serious adverse events highlighting unnecessary interventions for minor, self-limiting infusion reactions, which infrequently occur with intravenous iron administration. Recent data for the use of IV iron in a variety of clinic situations will be reviewed including women with heavy uterine bleeding, pregnancy, bariatric surgery, inflammatory bowel disease, and restless legs syndrome. Briefly discussed is the new frontier of IV iron's use in the prevention of acute (high altitude) mountain sickness. It is clear that in many clinical situations IV iron is a new and improved standard of care offering advantages over oral iron in efficacy, toxicity, and convenience to patients and health care providers.

Avanaki, A. R. N., Espig, K. S., Xthona, A., Lanciault, C., & Kimpe, T. R. L. (2017). *An observer model for quantifying panning artifacts in digital pathology*.

Typically, pathologists pan from one region of a slide to another, choosing areas of interest for closer inspection. Due to finite frame rate and imperfect zero-order hold reconstruction (i.e., the non-zero time to reach the target brightness after a change in pixel drive), panning in whole slide images (WSI) cause visual artifacts. It is important to study the impact of such artifacts since research suggests that 49% of navigation is conducted in low-power/overview with digital pathology (Molin et al., *Histopathology* 2015). In this paper, we explain what types of medical information may be harmed by panning artifacts, propose a method to simulate panning artifacts, and design an observer model to predict the impact of panning artifacts on typical human observers' performance in basic diagnostically relevant visual tasks. The proposed observer model is based on derivation of perceived object border maps from luminance and chrominance information and may be tuned to account for visual acuity of the human observer to be modeled. Our results suggest that increasing the contrast (e.g., using a wide gamut display) with a slow response panel may not mitigate the panning artifacts which mostly affect visual tasks involving spatial discrimination of objects (e.g., normal vs abnormal structure, cell type and spatial relationships between them, and low-power nuclear morphology), and that the panning artifacts worsen with increasing panning speed. The proposed methods may be used as building blocks in an automatic WSI quality assessment framework. © 2017 SPIE.

Avanaki, A. R. N., Lanciault, C., Espig, K. S., Xthona, A., & Kimpe, T. R. L. (2017). *Panning artifacts in digital pathology images*.

In making a pathologic diagnosis, a pathologist uses cognitive processes: perception, attention, memory, and search (Pena and Andrade-Filho, 2009). Typically, this involves focus while panning from one region of a slide to another, using either a microscope in a traditional workflow or software program and display in a digital pathology workflow (DICOM Standard Committee, 2010). We theorize that during panning operation, the pathologist receives information important to diagnosis efficiency and/or correctness. As compared to an optical microscope, panning in a digital pathology image involves some visual artifacts due to the following: (i) the frame rate is finite; (ii) time varying visual signals are reconstructed using imperfect zero-order hold. Specifically, after pixel's digital drive is changed, it takes time for a pixel to emit the expected amount of light. Previous work suggests that 49% of navigation is conducted in low-power/overview with digital pathology (Molin et al., 2015), but the influence of display factors has not been measured. We conducted a reader study to establish a relationship between display frame rate, panel response time, and threshold panning speed (above which the artifacts become noticeable). Our results suggest visual tasks that involve tissue structure are more impacted by the simulated panning artifacts than those that only involve color (e.g., staining intensity estimation), and that the panning artifacts versus normalized panning speed has a peak behavior which is surprising and may change for a diagnostic task. This is work in progress and our final findings should be considered in designing future digital pathology systems. © 2017 SPIE.

Aziz, M. F., Healy, D. W., Brambrink, A. M., & Kheterpal, S. (2017). **In Reply**. *Anesthesiology*, 127(1), 202-203.
doi:10.1097/aln.0000000000001692

Babaev, V. R., Yeung, M., Erbay, E., Ding, L., Zhang, Y., May, J. M., . . . Linton, M. F. (2016). **Jnk1 Deficiency in Hematopoietic Cells Suppresses Macrophage Apoptosis and Increases Atherosclerosis in Low-Density Lipoprotein Receptor Null Mice**. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 36(6), 1122-1131.
doi:10.1161/atvbaha.116.307580

OBJECTIVE: The c-Jun NH2-terminal kinases (JNK) are regulated by a wide variety of cellular stresses and have been implicated in apoptotic signaling. Macrophages express 2 JNK isoforms, JNK1 and JNK2, which may have different effects on cell survival and atherosclerosis. **APPROACH AND RESULTS:** To dissect the effect of macrophage JNK1 and JNK2 on early atherosclerosis, Ldlr(-/-) mice were reconstituted with wild-type, Jnk1(-/-), and Jnk2(-/-) hematopoietic cells and fed a high cholesterol diet. Jnk1(-/-)->Ldlr(-/-) mice have larger atherosclerotic lesions with more macrophages and fewer apoptotic cells than mice transplanted with wild-type or Jnk2(-/-) cells. Moreover, genetic ablation of JNK to a single allele (Jnk1(+/-)/Jnk2(-/-) or Jnk1(-/-)/Jnk2(+/-)) in marrow of Ldlr(-/-) recipients further increased atherosclerosis compared with Jnk1(-/-)->Ldlr(-/-) and wild-type->Ldlr(-/-) mice. In mouse macrophages, anisomycin-mediated JNK signaling antagonized Akt activity, and loss of Jnk1 gene obliterated this effect. Similarly, pharmacological inhibition of JNK1, but not JNK2, markedly reduced the antagonizing effect of JNK on Akt activity. Prolonged JNK signaling in the setting of endoplasmic reticulum stress gradually extinguished Akt and Bad activity in wild-type cells with markedly less effects in Jnk1(-/-) macrophages, which were also more resistant to apoptosis. Consequently, anisomycin increased and JNK1 inhibitors suppressed endoplasmic reticulum stress-mediated apoptosis in macrophages. We also found that genetic and pharmacological inhibition of phosphatase and tensin homolog abolished the JNK-mediated effects on Akt activity, indicating that phosphatase and tensin homolog mediates crosstalk between these pathways. **CONCLUSIONS:** Loss of Jnk1, but not Jnk2, in macrophages protects them from apoptosis, increasing cell survival, and this accelerates early atherosclerosis.

Badawy, S. M., Black, V., Meier, E. R., Myers, K. C., Pinkney, K., Hastings, C., . . . Vaiselbuh, S. R. (2017). **Early career mentoring through the American Society of Pediatric Hematology/Oncology: Lessons learned from a pilot program.** *Pediatr Blood Cancer*, 64(3). doi:10.1002/psc.26252

BACKGROUND: Effective networking and mentorship are critical determinants of career satisfaction and success in academic medicine. The American Society of Pediatric Hematology/Oncology (ASPHO) mentoring program was developed to support Early Career (EC) members. Herein, the authors report on the initial 2-year outcomes of this novel program. **PROCEDURE:** Mentees selected mentors with expertise in different subspecialties within the field from mentor profiles at the ASPHO Web site. Of 23 enrolled pairs, 19 mentors and 16 mentees completed electronic program feedback evaluations. The authors analyzed data collected between February 2013 and December 2014. The authors used descriptive statistics for categorical data and thematic analysis for qualitative data. **RESULTS:** The overall response rate was 76% (35/46). At the initiation of the relationship, career development and research planning were the most commonly identified goals for both mentors and mentees. Participants communicated by phone, e-mail, or met in-person at ASPHO annual meetings. Most mentor-mentee pairs were satisfied with the mentoring relationship, considered it a rewarding experience that justified their time and effort, achieved their goals in a timely manner with objective work products, and planned to continue the relationship. However, time constraints and infrequent communications remained a challenge. **CONCLUSIONS:** Participation in the ASPHO mentoring program suggests a clear benefit to a broad spectrum of ASPHO EC members with diverse personal and professional development needs. Efforts to expand the mentoring program are ongoing and focused on increasing enrollment of mentors to cover a wider diversity of career tracks/subspecialties and evaluating career and academic outcomes more objectively.

Barr, R. D., Ferrari, A., Ries, L., Whelan, J., & Bleyer, W. A. (2016). **Cancer in Adolescents and Young Adults: A Narrative Review of the Current Status and a View of the Future.** *JAMA Pediatr*, 170(5), 495-501. doi:10.1001/jamapediatrics.2015.4689

IMPORTANCE: Although cancer remains the most common cause of disease-related death in adolescents and young adults (AYAs) in high-income countries, their overall survival rates continue to increase and now exceed 80% at 5 years in several high-income countries. This has been accomplished through progressive improvements in active treatment and supportive care, although accrual rates to therapeutic clinical trials remain disappointing. Recognition of the unique distribution of diseases in the AYA population with cancer and

further understanding of the distinctive biology of cancers in AYAs will lead to continuing gains in clinical outcomes. **OBSERVATIONS:** Many of the challenges faced by AYAs with a diagnosis of malignant disease are shared by others with chronic medical conditions and even their healthy peers, such as a sense of invulnerability that may contribute to delays in diagnosis. A particular need for psychological support has been identified for AYAs with cancer, even after active therapy has been completed and especially in the context of palliative care. Notable needs also include fertility preservation and navigation through the multiple transitions in the cancer journey. Additionally, there is a "cost of cure." This is not only in the form of short-term, treatment-related morbidity and mortality but also in the burden of "late effects," including second cancers, that compromise quality of life and limit life expectancy. Establishing clinical programs devoted to AYAs with cancer, with complementary educational initiatives, will strengthen the advances made. It is anticipated that clinical trial accrual will increase substantially, providing further gains in survival. Likewise, addressing the challenges of survivorship, including secondary prevention of long-term morbidity and mortality, will lead to additional improvements in clinical outcomes. **CONCLUSIONS AND RELEVANCE:** Transferring this knowledge to the care of an estimated 1 million incident cases of cancer in AYAs worldwide, most of whom do not live in high-income countries, remains a considerable challenge.

Baum, S. J., Soffer, D., & Barton Duell, P. (2016). **Emerging Treatments for Heterozygous and Homozygous Familial Hypercholesterolemia.** *Reviews in Cardiovascular Medicine*, 17(1-2), 16-27.

Familial hypercholesterolemia (FH) is an autosomal co-dominant disorder marked by extremely high low-density lipoprotein (LDL) cholesterol levels and concomitant premature vascular disease. FH is caused by mutations that most commonly affect three genes integrally involved in the LDL receptor's ability to clear LDL particles from the circulation. Primary intervention efforts to lower LDL cholesterol have centered on therapies that upregulate the LDL receptor. Unfortunately, most patients are insufficiently responsive to traditional LDL-lowering medications. This article focuses primarily on the clinical management of homozygous FH.

Beach, M. C., Branyon, E., & Saha, S. (2017). **Diverse patient perspectives on respect in healthcare: A qualitative study.** *Patient Education and Counseling*. doi:10.1016/j.pec.2017.05.010

Background: The dominant view of respect in western bioethics focuses almost exclusively on respect for autonomy (or 'self-rule') as conceptualized primarily from the perspective of philosophers. We designed this study to understand, from the perspective of patients from different racial/ethnic groups, what it means for patients to be treated with respect in healthcare settings. **Methods:** We conducted focus groups with African American, Latino, and white patients in the Northwestern U.S. Focus groups were community-based and stratified by race and gender. We asked participants to describe respectful and disrespectful physician behaviors. We reviewed transcripts and coded for: 1) definitions of respect and 2) specific behaviors that convey respect or disrespect. **Results:** We conducted 26 focus groups, 5 each with African American men and women, 4 each with Latino men and women, and 4 each with white men and women. We identified two primary definitions of respect described by all three racial/ethnic groups. These were: 1) being treated like a person ("like you're a person not just a statistic, or another patient"), and 2) being treated as an equal ("treat me as an equal, like I matter"). When exploring specific behaviors that convey respect or disrespect, there were largely similar themes identified by all or most racial/ethnic groups. These were being known as a particular individual, avoidance of stereotyping, being treated politely, honest explanations of medical issues, and how lateness is handled. There were also some differences across racial/ethnic groups. The most prominent demonstration of respect mentioned among African American participants were for physicians to hear vs. dismiss what patients say and trusting the patient's knowledge of him/herself. The most prominent demonstration of respect discussed in the Latino focus groups was having the provider show concern by asking the questions about the patient's clinical condition. **Conclusions:** Our study found that patients have insights not included in common definitions of respect, and that deliberate inclusion of diverse participants increased the number of themes that emerged. Understanding what makes patients from different backgrounds feel respected and disrespected, from the perspectives of patients themselves, is vital to delivering care that is truly patient-centered. © 2017.

Berger, E. R., Clements, R. H., Morton, J. M., Huffman, K. M., Wolfe, B. M., Nguyen, N. T., . . . Hutter, M. M. (2016). **The Impact of Different Surgical Techniques on Outcomes in Laparoscopic Sleeve Gastrectomies: The First Report from the Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program (MBSAQIP)**. *Annals of Surgery, 264*(3), 464-473. doi:10.1097/sla.0000000000001851

OBJECTIVE: Questions remain regarding best surgical techniques to use for a laparoscopic sleeve gastrectomy (LSG) including the use of staple line reinforcement (SLR), bougie size (BS), and distance from the pylorus (DP) where the staple line is initiated. Our objectives were to assess the impact of these techniques on 30-day outcomes and to evaluate the impact of these techniques on weight loss and comorbidities at 1 year. **METHODS:** Using the MBSAQIP data registry, univariate analyses and hierarchical logistical regression models were developed to analyze outcomes for techniques of LSG at patient and surgeon-level. **RESULTS:** A total of 189,477 LSG operations were performed by 1634 surgeons at 720 centers from 2012 to 2014. Eighty percent of surgeons used SLR, 20% did not. SLR cases were associated with higher leak rates (0.96% vs 0.65%, odds ratio [OR] 1.20 95% confidence interval [CI] 1.00-1.43) and lower bleed rates (0.75% vs 1.00%, OR 0.74 95% CI 0.63-0.86) compared to no SLR at patient level. At the surgeon level, leak rates remained significant, but bleeding events became nonsignificant. BS ≥ 38 was associated with significantly lower leak rates compared to BS < 38 at patient and surgeon level (patient level: 0.80% vs 0.96%, OR 0.72, 95% CI 0.62-0.94; surgeon level: 0.84% vs 0.95%, OR 0.90, 95% CI 0.80-0.99). BS ≥ 40 was associated with increased weight loss. DP had no impact on leaks or bleeds but showed an increase in weight loss with increasing DP. **CONCLUSION:** LSG is a safe procedure with a low morbidity rate. SLR is associated with increased leak rates. A surgeon should consider risks, benefits, and costs of these surgical techniques when performing a LSG and selectively utilize those that, in their hands, minimize morbidity while maximizing clinical effectiveness.

Berland, M. A., Ulloa-Leal, C., Barria, M., Wright, H., Dissen, G. A., Silva, M. E., . . . Ratto, M. H. (2016). **Seminal Plasma Induces Ovulation in Llamas in the Absence of a Copulatory Stimulus: Role of Nerve Growth Factor as an Ovulation-Inducing Factor**. *Endocrinology, 157*(8), 3224-3232. doi:10.1210/en.2016-1310

Llamas are considered to be reflex ovulators. However, semen from these animals is reported to be rich in ovulation-inducing factor(s), one of which has been identified as nerve growth factor (NGF). These findings suggest that ovulation in llamas may be elicited by chemical signals contained in semen instead of being mediated by neural signals. The present study examines this notion. Llamas displaying a preovulatory follicle were assigned to four groups: group 1 received an intrauterine infusion (IUI) of PBS; group 2 received an IUI of seminal plasma; group 3 was mated to a male whose urethra had been surgically diverted (urethrostomized male); and group 4 was mated to an intact male. Ovulation (detected by ultrasonography) occurred only in llamas mated to an intact male or given an IUI of seminal plasma and was preceded by a surge in plasma LH levels initiated within an hour after coitus or IUI. In both ovulatory groups, circulating beta-NGF levels increased within 15 minutes after treatment, reaching values that were greater and more sustained in llamas mated with an intact male. These results demonstrate that llamas can be induced to ovulate by seminal plasma in the absence of copulation and that copulation alone cannot elicit ovulation in the absence of seminal plasma. In addition, our results implicate beta-NGF as an important mediator of seminal plasma-induced ovulation in llamas because ovulation does not occur if beta-NGF levels do not increase in the bloodstream, a change that occurs promptly after copulation with an intact male or IUI of seminal plasma.

Bethea, C. L., Mueller, K., Reddy, A. P., Kohama, S. G., & Urbanski, H. F. (2017). **Effects of obesogenic diet and estradiol on dorsal raphe gene expression in old female macaques**. *PLoS ONE, 12*(6), e0178788. doi:10.1371/journal.pone.0178788

The beneficial effects of bioidentical ovarian steroid hormone therapy (HT) during the perimenopause are gaining recognition. However, the positive effects of estrogen (E) plus or minus progesterone (P) administration to ovariectomized (Ovx) lab animals were recognized in multiple systems for years before clinical trials could

adequately duplicate the results. Moreover, very large numbers of women are often needed to find statistically significant results in clinical trials of HT; and there are still opposing results being published, especially in neural and cardiovascular systems. One of the obvious differences between human and animal studies is diet. Laboratory animals are fed a diet that is low in fat and refined sugar, but high in micronutrients. In the US, a large portion of the population eats what is known as a "western style diet" or WSD that provides calories from 36% fat, 44% carbohydrates (includes 18.5% sugars) and 18% protein. Unfortunately, obesity and diabetes have reached epidemic proportions and the percentage of obese women in clinical trials may be overlooked. We questioned whether WSD and obesity could decrease the positive neural effects of estradiol (E) in the serotonin system of old macaques that were surgically menopausal. Old ova-hysterectomized female monkeys were fed WSD for 2.5 years, and treated with placebo, Immediate E (ImE) or Delayed E (DE). Compared to old Ovx macaques on primate chow and treated with placebo or E, the WSD-fed monkeys exhibited greater individual variance and blunted responses to E-treatment in the expression of genes related to serotonin neurotransmission, CRH components in the midbrain, synapse assembly, DNA repair, protein folding, ubiquitylation, transport and neurodegeneration. For many of the genes examined, transcript abundance was lower in WSD-fed than chow-fed monkeys. In summary, an obesogenic diet for 2.5 years in old surgically menopausal macaques blunted or increased variability in E-induced gene expression in the dorsal raphe. These results suggest that with regard to function and viability in the dorsal raphe, HT may not be as beneficial for obese women as normal weight women.

Bleyer, A., Barr, R., Ries, L., Whelan, J., & Ferrari, A. (2017) Erratum to: Cancer in adolescents and young adults (Pediatric oncology, 10.1007/978-3-319-33679-4). *Pediatric Oncology* (pp. E1): Springer Verlag.

In the original version for chapter 13, the chapter author name was wrongly given as James Trocoli. The name of the author should be read: James V. Tricoli In the original version for chapter 34, the chapter title was wrongly given as DRAFT: AYA Advocacy in Action-Achievements, Lessons, and Challenges from a Global Movement for Change The correct chapter title should be: AYA Advocacy in Action-Achievements, Lessons, and Challenges from a Global Movement for Change The above mentioned corrections also updated in Table of Contents. © Springer International Publishing AG 2017.

Bogdanova, Y. A., Schultz, C., & Belousov, V. V. (2017). **Local Generation and Imaging of Hydrogen Peroxide in Living Cells**. *Current Protocols in Chemical Biology*, 9(2), 117-127. doi:10.1002/cpch.20

Described here is a localized H₂ O₂ generation-detection system consisting of a yeast D-amino acid oxidase (DAAO) and two spectrally distinct variants of biosensor, HyPer2 and HyPerRed based on circularly permuted yellow and red fluorescent proteins, respectively, which enables spatiotemporal production and examination of the intracellular H₂ O₂ dynamics. The protocol describes using this system in a simple cell culture model. We provide detailed instructions on imaging of H₂ O₂ generated by the activated DAAO. The system can be easily optimized for various combinations of cell types, conditions and DAAO/sensor subcellular localizations. (c) 2017 by John Wiley & Sons, Inc.

Broeckel, R., Fox, J. M., Haese, N., Kreklywich, C. N., Sukulpovi-Petty, S., Legasse, A., . . . Streblow, D. N. (2017). **Therapeutic administration of a recombinant human monoclonal antibody reduces the severity of chikungunya virus disease in rhesus macaques**. *PLoS Negl Trop Dis*, 11(6), e0005637. doi:10.1371/journal.pntd.0005637

Chikungunya virus (CHIKV) is a mosquito-borne virus that causes a febrile syndrome in humans associated with acute and chronic debilitating joint and muscle pain. Currently no licensed vaccines or therapeutics are available to prevent or treat CHIKV infections. We recently isolated a panel of potentially neutralizing human monoclonal antibodies (mAbs), one (4N12) of which exhibited prophylactic and post-exposure therapeutic activity against CHIKV in immunocompromised mice. Here, we describe the development of an engineered CHIKV

mAb, designated SVIR001, that has similar antigen binding and neutralization profiles to its parent, 4N12. Because therapeutic administration of SVIR001 in immunocompetent mice significantly reduced viral load in joint tissues, we evaluated its efficacy in a rhesus macaque model of CHIKV infection. Rhesus macaques that were treated after infection with SVIR001 showed rapid elimination of viremia and less severe joint infiltration and disease compared to animals treated with SVIR002, an isotype control mAb. SVIR001 reduced viral burden at the site of infection and at distant sites and also diminished the numbers of activated innate immune cells and levels of pro-inflammatory cytokines and chemokines. SVIR001 therapy; however, did not substantively reduce the induction of CHIKV-specific B or T cell responses. Collectively, these results show promising therapeutic activity of a human anti-CHIKV mAb in rhesus macaques and provide proof-of-principle for its possible use in humans to treat active CHIKV infections.

Brookfield, K. F., Elkomy, M., Su, F., Drover, D. R., & Carvalho, B. (2017). **Optimization of Maternal Magnesium Sulfate Administration for Fetal Neuroprotection: Application of a Prospectively Constructed Pharmacokinetic Model to the BEAM Cohort.** *Journal of Clinical Pharmacology*. doi:10.1002/jcph.941

The aim of the study was to identify the optimal therapeutic maternal magnesium drug exposure and maternal serum concentration to prevent cerebral palsy in the extremely preterm fetus. We applied a previously constructed pharmacokinetic model adjusted for indication to a large cohort of pregnant women receiving magnesium sulfate to prevent cerebral palsy in their preterm offspring at 20 different US academic centers between December 1997 and May 2004. We simulated the population-based individual maternal serum magnesium concentration at the time of delivery and the total magnesium dose for each woman who received magnesium sulfate to determine the relationship between maternal serum magnesium level at the time of delivery and the development of cerebral palsy. Among 1905 women who met inclusion criteria, the incidence of cerebral palsy in the cohort was 3.6% for women who had received magnesium sulfate and 6.4% for controls. The simulated maternal serum concentration at delivery associated with the lowest probability of delivering an infant with cerebral palsy was 4.1 mg/dL (95%CI 3.7 to 4.4). Our population-based estimates of magnesium disposition suggest that to optimize fetal neuroprotection and prevent cerebral palsy, magnesium sulfate administration should target a maternal serum magnesium level between 3.7 and 4.4 mg/dL at delivery. © 2017, The American College of Clinical Pharmacology.

Brooks, S. C., Schmicker, R. H., Cheskes, S., Christenson, J., Craig, A., Daya, M., . . . Morrison, L. J. (2017). **Variability in the initiation of resuscitation attempts by emergency medical services personnel during out-of-hospital cardiac arrest.** *Resuscitation*. doi:10.1016/j.resuscitation.2017.06.009

BACKGROUND: Some patients with out-of-hospital cardiac arrest (OHCA) assessed by emergency medical services (EMS) do not receive attempts at resuscitation on the basis of perceived futility. **AIMS:** 1) To measure variability in the initiation of resuscitation attempts in EMS-assessed OHCA patients across EMS agencies, 2) to evaluate the association between selected EMS agency characteristics and the proportion of patients receiving resuscitation attempts, and 3) to evaluate the association between proportion receiving resuscitation attempts and survival. **METHODS:** A retrospective cohort study using data from 129 EMS agencies participating in the Resuscitation Outcomes Consortium (ROC) epidemiologic registry (EPISTRY) - Cardiac Arrest from 12/01/2005 to 12/31/2010. We included non-traumatic OHCA patients assessed by EMS. **RESULTS:** We included 86,912 OHCA patients. Overall, 54.8% had resuscitation attempted by EMS providers, varying from 23.9% to 100% ($p < 0.001$) across EMS agencies. The proportion of patients receiving a resuscitation attempt was 7.87% less (95% CI 3.73-12.0) among agencies with longer average response intervals (≥ 6 minutes) compared with shorter average response intervals (< 6 minutes) and 16.9% less (95% CI 11.9-21.9) among agencies with higher levels of advanced life support (ALS) availability ($\geq 50\%$ of available units) compared with lower levels of ALS availability ($< 50\%$ of available units). There was a moderate positive correlation between the proportion of patients with resuscitation attempts and survival to hospital discharge ($r = 0.54$, $p < 0.001$). **CONCLUSIONS:** The proportion of patients with OHCA who receive resuscitation attempts is variable across EMS agencies and is associated with EMS response interval, ALS unit

availability and geographic region. On average, survival was higher among EMS agencies more likely to initiate resuscitation.

Cahoon, E. K., Preston, D. L., Pierce, D. A., Grant, E., Brenner, A. V., Mabuchi, K., . . . Ozasa, K. (2017). **Lung, Laryngeal and Other Respiratory Cancer Incidence among Japanese Atomic Bomb Survivors: An Updated Analysis from 1958 through 2009.** *Radiation Research*, 187(5), 538-548. doi:10.1667/RR14583.1

The Life Span Study (LSS) of Japanese atomic bomb survivors is comprised of a large, population-based cohort offering one of the best opportunities to study the relationship between exposure to radiation and incidence of respiratory cancers. Risks of lung, laryngeal and other cancers of the respiratory system were evaluated among 105,444 LSS subjects followed from 1958 to 2009. During this period, we identified 2,446 lung, 180 laryngeal and 115 other respiratory (trachea, mediastinum and other ill-defined sites) first primary incident cancer cases. Ten additional years of follow-up, improved radiation dose estimates, revised smoking data, and updated migration information were used to investigate the joint effects of radiation and smoking using Poisson regression methods. For nonsmokers, the sex-averaged excess relative risk per Gy (ERR/Gy) for lung cancer (at age 70 after radiation exposure at age 30) was estimated as 0.81 (95% CI: 0.51, 1.18) with a female-to-male ratio of 2.83. There was no evidence of curvature in the radiation dose-response relationship overall or by sex. Lung cancer risks increased with pack-years of smoking and decreased with time since quitting smoking at any level of radiation exposure. Similar to the previously reported study, which followed cohort members through 1999, the ERR/Gy for lung cancer was significantly higher for low-to-moderate smokers than for heavy smokers, with little evidence of any radiation-associated excess risk in heavy smokers. Of 2,446 lung cancer cases, 113 (5%) could be attributed to radiation exposure. Of the 1,165 lung cancer cases occurring among smokers, 886 (76%) could be attributed to smoking. While there was little evidence of a radiation effect for laryngeal cancer, a nonsignificantly elevated risk of other respiratory cancers was observed. However, significant smoking effects were observed for both laryngeal (ERR per 50 pack-years = 23.57; 95% CI: 8.44, 71.05) and other respiratory cancers (ERR per 50 pack-years = 1.21; 95% CI: 0.10, 3.25). © 2017 by Radiation Research Society.

Cajaiba, M. M., North, P. E., Gong, S., Dickman, P. S., Mroczek-Musulman, E., Sauer, D. A., & Perlman, E. J. (2017). **Congenital Capillary Proliferation of the Kidney: A Distinctive Renal Vascular Lesion of Childhood.** *Human Pathology*. doi:10.1016/j.humpath.2017.05.018

Renal vascular lesions (RVL) are rare and their morphological spectrum remains largely unknown, particularly in children. In this study, we characterize the clinicopathological features of RVL in a cohort of twelve children. Seven lesions were classified as previously recognized entities: vascular malformations (four), papillary endothelial hyperplasia (two), and pyogenic granuloma (lobular capillary hemangioma) (one). An eighth lesion showed nonspecific findings which were interpreted as reactive during our review. The remaining four cases presented either prenatally, at birth, or shortly after birth and were morphologically similar. These were characterized by a peculiar pattern of capillary proliferation with entrapment of native renal structures, variable amounts of extramedullary hematopoiesis and reactive lymphocytes, foci of infarction and hemorrhage, and the presence of feeding and draining vessels at their periphery. To our knowledge, this represents a previously undescribed congenital vascular lesion involving the kidney, which we have descriptively and provisionally termed congenital capillary proliferation of the kidney (CCPK). While it is unclear whether CCPK represents a malformation or neoplastic proliferation, it shows overlapping features with congenital hemangioma of the liver (solitary congenital hepatic hemangioma - SCHH) and congenital nonprogressive hemangioma (CNH) of the skin and soft tissue, suggesting a possible common pathogenesis among these three entities.

Camino, A., Jia, Y., Liu, G., Wang, J., & Huang, D. (2017). **Regression-based algorithm for bulk motion subtraction in optical coherence tomography angiography.** *Biomed Opt Express*, 8(6). doi:10.1364/BOE.8.003053

We developed an algorithm to remove decorrelation noise due to bulk motion in optical coherence tomography angiography (OCTA) of the posterior eye. In this algorithm, OCTA B-frames were divided into segments within which the bulk motion velocity could be assumed to be constant. This velocity was recovered using linear regression of decorrelation versus the logarithm of reflectance in axial lines (A-lines) identified as bulk tissue by percentile analysis. The fitting parameters were used to calculate a reflectance-adjusted upper bound threshold for bulk motion decorrelation. Below this threshold, voxels are identified as non-flow tissue, their flow values are set to zeros. Above this threshold, the voxels are identified as flow voxels and bulk motion velocity is subtracted from each using a nonlinear decorrelation-velocity relationship previously established in laboratory flow phantoms. Compared to the simpler median-subtraction method, the regression-based bulk motion subtraction improved angiogram signal-to-noise ratio, contrast, vessel density repeatability, and bulk motion noise cleanup in the foveal avascular zone, while preserving the connectivity of the vascular networks in the angiogram. © 2017 Optical Society of America.

Castle, J. R., DeVries, J. H., & Kovatchev, B. (2017). **Future of automated insulin delivery systems.** *Diabetes Technology and Therapeutics, 19*, S67-S72. doi:10.1089/dia.2017.0012

Advances in continuous glucose monitoring (CGM) have brought on a paradigm shift in the management of type 1 diabetes. These advances have enabled the automation of insulin delivery, where an algorithm determines the insulin delivery rate in response to the CGM values. There are multiple automated insulin delivery (AID) systems in development. A system that automates basal insulin delivery has already received Food and Drug Administration approval, and more systems are likely to follow. As the field of AID matures, future systems may incorporate additional hormones and/or multiple inputs, such as activity level. All AID systems are impacted by CGM accuracy and future CGM devices must be shown to be sufficiently accurate to be safely incorporated into AID. In this article, we summarize recent achievements in AID development, with a special emphasis on CGM sensor performance, and discuss the future of AID systems from the point of view of their input-output characteristics, form factor, and adaptability. © Copyright 2017, Mary Ann Liebert, Inc.

Caughey, A. B. (2017). **Gestational Weight Gain and Outcomes for Mothers and Infants.** *Jama, 317*(21), 2175-2176. doi:10.1001/jama.2017.6265

Chan, T. M., Grock, A., Paddock, M., Kulasegaram, K., Yarris, L. M., & Lin, M. (2016). **Examining Reliability and Validity of an Online Score (ALiEM AIR) for Rating Free Open Access Medical Education Resources.** *Ann Emerg Med, 68*(6), 729-735. doi:10.1016/j.annemergmed.2016.02.018

STUDY OBJECTIVE: Since 2014, Academic Life in Emergency Medicine (ALiEM) has used the Approved Instructional Resources (AIR) score to critically appraise online content. The primary goals of this study are to determine the interrater reliability (IRR) of the ALiEM AIR rating score and determine its correlation with expert educator gestalt. We also determine the minimum number of educator-raters needed to achieve acceptable reliability. **METHODS:** Eight educators each rated 83 online educational posts with the ALiEM AIR scale. Items include accuracy, usage of evidence-based medicine, referencing, utility, and the Best Evidence in Emergency Medicine rating score. A generalizability study was conducted to determine IRR and rating variance contributions of facets such as rater, blogs, posts, and topic. A randomized selection of 40 blog posts previously rated through ALiEM AIR was then rated again by a blinded group of expert medical educators according to their gestalt. Their gestalt impression was subsequently correlated with the ALiEM AIR score. **RESULTS:** The IRR for the ALiEM AIR rating scale was 0.81 during the 6-month pilot period. Decision studies showed that at least 9 raters were required to achieve this reliability. Spearman correlations between mean AIR score and the mean expert gestalt ratings were 0.40 for recommendation for learners and 0.35 for their colleagues. **CONCLUSION:** The ALiEM AIR scale is a moderately to highly reliable, 5-question tool when used by medical educators for rating online resources. The score displays a fair correlation with expert educator gestalt in regard to the quality of the resources. The score displays a fair correlation with educator gestalt.

Chang, R., Holcomb, J. B., Johansson, P. I., Pati, S., Schreiber, M. A., & Wade, C. E. (2017). **Plasma Resuscitation Improved Survival in a Cecal Ligation and Puncture Rat Model of Sepsis.** *Shock*. doi:10.1097/SHK.0000000000000918

BACKGROUND: The paradigm shift from crystalloid to plasma resuscitation of traumatic hemorrhagic shock has improved patient outcomes due in part to plasma-mediated reversal of catecholamine and inflammation-induced endothelial injury, decreasing vascular permeability and attenuating organ injury. Since sepsis induces a similar endothelial injury as seen in hemorrhage, we hypothesized that plasma resuscitation would increase 48-hour survival in a rat sepsis model. **METHODS:** Adult male Sprague-Dawley rats (375–425g) were subjected to 35% cecal ligation and puncture (CLP) (t=0h). Twenty-two hours post-CLP and prior to resuscitation (t=22h), animals were randomized to resuscitation with normal saline (NS, 10cc/kg/hr) or pooled rat fresh frozen plasma (FFP, 3.33cc/kg/hr). Resuscitation under general anesthesia proceeded for the next six hours (t=22h to t=28h); lactate was checked every 2 hours, and fluid volumes were titrated based on lactate clearance. Blood samples were obtained before (t=22h) and after resuscitation (t=28h), and at death or study conclusion. Lung specimens were obtained for calculation of wet-to-dry weight ratio. Fisher's exact test was used to analyze the primary outcome of 48-hour survival. ANOVA with repeated measures was used to analyze the effect of FFP versus NS resuscitation on blood gas, electrolytes, blood urea nitrogen (BUN), creatinine, interleukin (IL)-6, IL-10, catecholamines, and syndecan-1 (marker for endothelial injury). A two-tailed alpha level of <0.05 was used for all statistical tests. **RESULTS:** Thirty-three animals were studied: 14 FFP, 14 NS, and 5 sham. Post-CLP but pre-resuscitation (t=22h) variables between FFP and NS animals were similar and significantly deranged compared to sham animals. FFP significantly increased 48-hour survival compared to NS (n=8 [57%] vs n=2 [14%]), attenuated the post-resuscitation (t=28h) levels of epinephrine (mean 2.2 vs 7.0ng/ml), norepinephrine, (3.8 vs 8.9ng/ml), IL-6 (3.8 vs 18.7ng/ml), and syndecan-1 (21.8 vs 31.0ng/ml) (all p<0.05), improved the post-resuscitation PO2 to FiO2 ratio (353 vs 151), and reduced the pulmonary wet-to-dry weight ratio (5.28 vs 5.94) (all p<0.05). **CONCLUSION:** Compared to crystalloid, plasma resuscitation increased 48-hour survival in a rat sepsis model, improved pulmonary function and decreased pulmonary edema, and attenuated markers for inflammation, endothelial injury, and catecholamines. © 2017 by the Shock Society

Chang, Y. H., Thibault, G., Johnson, B., Margolin, A., & Gray, J. W. (2017). *Integrative analysis on histopathological image for identifying cellular heterogeneity.*

This study has brought together image processing, clustering and spatial pattern analysis to quantitatively analyze hematoxylin and eosin-stained (H&E) tissue sections. A mixture of tumor and normal cells (intratumoral heterogeneity) as well as complex tissue architectures of most samples complicate the interpretation of their cytological profiles. To address these challenges, we develop a simple but effective methodology for quantitative analysis for H&E section. We adopt comparative analyses of spatial point patterns to characterize spatial distribution of different nuclei types and complement cellular characteristics analysis. We demonstrate that tumor and normal cell regions exhibit significant differences of lymphocytes spatial distribution or lymphocyte infiltration pattern. © 2017 SPIE.

Chao, B., Li, B. X., & Xiao, X. (2017). **Design, synthesis and evaluation of antitumor acylated monoaminopyrroloquinazolines.** *Bioorg Med Chem Lett*, 27(14), 3107-3110. doi:10.1016/j.bmcl.2017.05.038

Pyrrroloquinazoline is a privileged chemical scaffold with diverse biological activities. We recently described a series of N-3 acylated 1,3-diaminopyrroloquinazolines with potent anticancer activities. The N-1 primary amino group in 1,3-diaminopyrroloquinazoline is critical for its inhibitory activity against dihydrofolate reductase (DHFR). In order to design out this unnecessary DHFR inhibition activity and further expand the chemical space associated with pyrroloquinazoline, we removed the N-1 primary amino group. In this report, we describe our design and synthesis of a series of N-3 acylated monoaminopyrroloquinazolines. Biological evaluation of

these compounds identified a naphthamide 4a as a potent anticancer agent (GI50=88-200nM), suggesting that removing the N-1 primary amino group in 1,3-diaminopyrroloquinazoline is a useful chemical modification that can be introduced to improve the anticancer activity.

Clark, A. T., Gkountela, S., Chen, D., Liu, W., Sosa, E., Sukhwani, M., . . . Orwig, K. E. (2016). **Primate Primordial Germ Cells Acquire Transplantation Potential by Carnegie Stage 23**. *Stem Cell Reports*. doi:10.1016/j.stemcr.2017.05.002

Primordial germ cells (PGCs) are the earliest embryonic progenitors in the germline. Correct formation of PGCs is critical to reproductive health as an adult. Recent work has shown that primate PGCs can be differentiated from pluripotent stem cells; however, a bioassay that supports their identity as transplantable germ cells has not been reported. Here, we adopted a xenotransplantation assay by transplanting single-cell suspensions of human and nonhuman primate embryonic *Macaca mulatta* (rhesus macaque) testes containing PGCs into the seminiferous tubules of adult busulfan-treated nude mice. We discovered that both human and nonhuman primate embryonic testis are xenotransplantable, generating colonies while not generating tumors. Taken together, this work provides two critical references (molecular and functional) for defining transplantable primate PGCs. These results provide a blueprint for differentiating pluripotent stem cells to transplantable PGC-like cells in a species that is amenable to transplantation and fertility studies. In this article, Clark and colleagues examined the molecular identity and xenotransplantability of primate PGCs in the seminiferous tubules of the mouse testis. This work revealed that following transplant, human and nonhuman primate PGCs generated colonies while not generating tumors. This work establishes a new *in vivo* test for confirming putative PGC-like cell differentiation from pluripotent stem cells. © 2017 The Author(s).

Colgan, D. D., Wahbeh, H., Pleet, M., Besler, K., & Christopher, M. (2017). **A Qualitative Study of Mindfulness Among Veterans With Posttraumatic Stress Disorder: Practices Differentially Affect Symptoms, Aspects of Well-Being, and Potential Mechanisms of Action**. *Journal of Evidence-Based Complementary and Alternative Medicine*, 22(3), 482-493. doi:10.1177/2156587216684999

This qualitative study explored and compared the subjective experiences of 102 veterans with posttraumatic stress disorder (PTSD) who were randomly assigned to 1 of 4 arms: (a) body scan, (b) mindful breathing, (c) slow breathing, or (d) sitting quietly. Qualitative data were obtained via semistructured interviews following the intervention and analyzed using conventional content analysis. The percentage of participants within each intervention who endorsed a specific theme was calculated. Two-proportion z tests were then calculated to determine if the differences among themes endorsed in specific groups were statistically significant. Six core themes emerged from analysis of participant responses across the 4 groups: (a) enhanced present moment awareness, (b) increased nonreactivity, (c) increased nonjudgmental acceptance, (d) decreased physiological arousal and stress reactivity, (e) increased active coping skills, and (f) greater relaxation. More participants in the mindfulness intervention groups reported improvement in PTSD symptoms when compared to participants in non-mindfulness groups. Different types of intervention targeted different symptoms and aspects of well-being. Furthermore, type of intervention may have also differentially targeted potential mechanisms of action. This article highlights the importance of employing both quantitative and qualitative research methods when investigating the dynamic process of mindfulness and may inform how practices can be tailored to the needs of the veteran with PTSD. © 2017, © The Author(s) 2017.

Conte, D., Favero, T. G., Niederhausen, M., Capranica, L., & Tessitore, A. (2017). **Determinants of the effectiveness of fast break actions in elite and sub-elite Italian men's basketball games**. *Biology of Sport*, 34(2), 177-183. doi:10.5114/biolport.2017.65337

The aim of this study was to examine the determinants of successful and unsuccessful fast-break (FB) actions in elite and sub-elite basketball games. Fifteen 1st-division (elite) and fifteen 3rd-division (sub-elite) Italian men's

championship games were analysed across two seasons (2012/2013 and 2013/2014). A binary logistic regression analysis was performed, and the fast-break outcome (successful vs. unsuccessful) was adopted as the dependent variable separately in both elite and sub-elite games. FB execution (initiation, advance and completion phases), typology (primary and secondary break) and the number of players involved (equal number or superiority) were used as independent variables. The results showed that the rate of success of FB actions was 63.5% and 59.7% in elite and sub-elite games, respectively. Moreover, successful FBs were more likely to be completed in the lane in relation to unsuccessful ones in both elite and sub-elite games ($p < 0.05$). Finally, descriptive statistics showed that both elite and sub-elite teams executed FBs similarly. This study highlighted that completion zone was the only predictor of a successful fast break in basketball, while the typology and number of players involved did not predict fast break effectiveness. Moreover, elite and sub-elite teams executed fast break actions similarly. These findings might be useful for basketball coaches to optimize the training of FB actions.

Crowson, M. G., Rocke, D. J., Hoang, J. K., Weissman, J. L., & Kaylie, D. M. (2017). **Cost-effectiveness analysis of a non-contrast screening MRI protocol for vestibular schwannoma in patients with asymmetric sensorineural hearing loss.** *Neuroradiology*. doi:10.1007/s00234-017-1859-2

PURPOSE: We aimed to determine if a non-contrast screening MRI is cost-effective compared to a full MRI protocol with contrast for the evaluation of vestibular schwannomas. **METHODS:** A decision tree was constructed to evaluate full MRI and screening MRI strategies for patients with asymmetric sensorineural hearing loss. If a patient were to have a positive screening MRI, s/he received a full MRI. Vestibular schwannoma prevalence, MRI specificity and sensitivity, and gadolinium anaphylaxis incidence were obtained through literature review. Institutional charge data were obtained using representative patient cohorts. One-way and probabilistic sensitivity analyses were completed to determine CE model threshold points for MRI performance characteristics and charges. **RESULTS:** The mean charge for a full MRI with contrast was significantly higher than a screening MRI (\$4089 +/- 1086 versus \$2872 +/- 741; $p < 0.05$). The screening MRI protocol was more cost-effective than a full MRI protocol with a willingness-to-pay from \$0 to 20,000 USD. Sensitivity analyses determined that the screening protocol dominated when the screening MRI charge was less than \$4678, and the imaging specificity exceeded 78.2%. The screening MRI protocol also dominated when vestibular schwannoma prevalence was varied between 0 and 1000 in 10,000 people. **CONCLUSION:** A screening MRI protocol is more cost-effective than a full MRI with contrast in the diagnostic evaluation of a vestibular schwannoma. A screening MRI likely also confers benefits of shorter exam time and no contrast use. Further investigation is needed to confirm the relative performance of screening protocols for vestibular schwannomas.

Cuellar-Partida, G., Lu, Y., Dixon, S. C., Fasching, P. A., Hein, A., Burghaus, S., . . . MacGregor, S. (2016). **Assessing the genetic architecture of epithelial ovarian cancer histological subtypes.** *Human Genetics*, 135(7), 741-756. doi:10.1007/s00439-016-1663-9

Epithelial ovarian cancer (EOC) is one of the deadliest common cancers. The five most common types of disease are high-grade and low-grade serous, endometrioid, mucinous and clear cell carcinoma. Each of these subtypes present distinct molecular pathogeneses and sensitivities to treatments. Recent studies show that certain genetic variants confer susceptibility to all subtypes while other variants are subtype-specific. Here, we perform an extensive analysis of the genetic architecture of EOC subtypes. To this end, we used data of 10,014 invasive EOC patients and 21,233 controls from the Ovarian Cancer Association Consortium genotyped in the iCOGS array (211,155 SNPs). We estimate the array heritability (attributable to variants tagged on arrays) of each subtype and their genetic correlations. We also look for genetic overlaps with factors such as obesity, smoking behaviors, diabetes, age at menarche and height. We estimated the array heritabilities of high-grade serous disease ([Formula: see text] = 8.8 +/- 1.1 %), endometrioid ([Formula: see text] = 3.2 +/- 1.6 %), clear cell ([Formula: see text] = 6.7 +/- 3.3 %) and all EOC ([Formula: see text] = 5.6 +/- 0.6 %). Known associated loci contributed approximately 40 % of the total array heritability for each subtype. The contribution of each chromosome to the total heritability was not proportional to chromosome size.

Through bivariate and cross-trait LD score regression, we found evidence of shared genetic backgrounds between the three high-grade subtypes: serous, endometrioid and undifferentiated. Finally, we found significant genetic correlations of all EOC with diabetes and obesity using a polygenic prediction approach.

Da Conceição, E. P. S., Madden, C. J., & Morrison, S. F. (2017). **Glycinergic inhibition of bat sympathetic premotor neurons in rostral raphe pallidus.** *American Journal of Physiology - Regulatory Integrative and Comparative Physiology*, 312(6), R919-R926. doi:10.1152/ajpregu.00551.2016

The rostral raphe pallidus (rRPa) contains sympathetic premotor neurons controlling thermogenesis in brown adipose tissue (BAT). We sought to determine whether a tonic activation of glycineA receptors (GlyAR) in the rRPa contributes to the inhibitory regulation of BAT sympathetic nerve activity (SNA) and of cardiovascular parameters in anesthetized rats. Nano-injection of the GlyAR antagonist, strychnine (STR), into the rRPa of intact rats increased BAT SNA (peak: +495%), BAT temperature (TBAT, +1.1°C), expired CO₂ (+0.4%), core body temperature (TCORE, +0.2°C), mean arterial pressure (MAP, +4 mmHg), and heart rate (HR, +57 beats/min). STR into rRPa in rats with a postdorsomedial hypothalamus transection produced similar increases in BAT thermogenic and cardiovascular parameters. Glycine nano-injection into the rRPa evoked a potent inhibition of the cooling-evoked increases in BAT SNA (nadir: -74%), TBAT (-0.2°C), TCORE (-0.2°C), expired CO₂ (-0.2%), MAP (-8 mmHg), and HR (-22 beats/min) but had no effect on the increases in these variables evoked by STR nano-injection into rRPa. Nano-injection of GABA into the rRPa inhibited the STR-evoked BAT SNA (nadir: -86%) and reduced the expired CO₂ (-0.4%). Blockade of glutamate receptors in rRPa reduced the STR-evoked increases in BAT SNA (nadir: -61%), TBAT (-0.5°C), expired CO₂ (-0.3%), MAP (-9 mmHg), and HR (-33 beats/min). We conclude that a tonically active glycinergic input to the rRPa contributes to the inhibitory regulation of the discharge of BAT sympathetic premotor neurons and of BAT thermogenesis and energy expenditure. © 2017 the American Physiological Society.

Davis, M. Y., Johnson, C. O., Leverenz, J. B., Weintraub, D., Trojanowski, J. Q., Chen-Plotkin, A., . . . Zabetian, C. P. (2016). **Association of GBA Mutations and the E326K Polymorphism With Motor and Cognitive Progression in Parkinson Disease.** *JAMA Neurol*, 73(10), 1217-1224. doi:10.1001/jamaneurol.2016.2245

Importance: Parkinson disease (PD) is heterogeneous in symptom manifestation and rate of progression. Identifying factors that influence disease progression could provide mechanistic insight, improve prognostic accuracy, and elucidate novel therapeutic targets. Objective: To determine whether GBA mutations and the E326K polymorphism modify PD symptom progression. Design, Setting, and Participants: The entire GBA coding region was screened for mutations and E326K in 740 patients with PD enrolled at 7 sites from the PD Cognitive Genetics Consortium. Detailed longitudinal motor and cognitive assessments were performed with patients in the on state. Main Outcomes and Measures: Linear regression was used to test for an association between GBA genotype and motor progression, with the Movement Disorder Society-sponsored version of the Unified Parkinson's Disease Rating Scale Part III (MDS-UPDRS III) score at the last assessment as the outcome and GBA genotype as the independent variable, with adjustment for levodopa equivalent dose, sex, age, disease duration, MDS-UPDRS III score at the first assessment, duration of follow-up, and site. Similar methods were used to examine the association between genotype and tremor and postural instability and gait difficulty (PIGD) scores. To examine the effect of GBA genotype on cognitive progression, patients were classified into those with conversion to mild cognitive impairment or dementia during the study (progression) and those without progression. The association between GBA genotype and progression status was then tested using logistic regression, adjusting for sex, age, disease duration, duration of follow-up, years of education, and site. Results: Of the total sample of 733 patients who underwent successful genotyping, 226 (30.8%) were women and 507 (69.2%) were men (mean [SD] age, 68.1 [8.8] years). The mean (SD) duration of follow-up was 3.0 (1.7) years. GBA mutations (beta = 4.65; 95% CI, 1.72-7.58; P = .002), E326K (beta = 3.42; 95% CI, 0.66-6.17; P = .02), and GBA variants combined as a single group (beta = 4.01; 95% CI, 1.95-6.07; P = 1.5 x 10⁻⁴) were associated with a more rapid decline in MDS-UPDRS III score. Combined GBA variants (beta = 0.38; 95% CI, 0.23-0.53; P = .01) and E326K (beta = 0.64; 95% CI, 0.43-0.86; P = .002) were associated with faster progression in PIGD scores, but not in tremor scores. A significantly

higher proportion of E326K carriers (10 of 21 [47.6%]; $P = .01$) and GBA variant carriers (15 of 39 [38.5%]; $P = .04$) progressed to mild cognitive impairment or dementia. Conclusions and Relevance: GBA variants predict a more rapid progression of cognitive dysfunction and motor symptoms in patients with PD, with a greater effect on PIGD than tremor. Thus, GBA variants influence the heterogeneity in symptom progression observed in PD.

Davulcu, O., Peng, Y., Brüscheiler, R., Skalicky, J. J., & Chapman, M. S. (2017). **Elevated μ s-ms timescale backbone dynamics in the transition state analog form of arginine kinase.** *Journal of Structural Biology*. doi:10.1016/j.jsb.2017.05.002

Arginine kinase catalyzes reversible phosphoryl transfer between arginine and ATP. Crystal structures of arginine kinase in an open, substrate-free form and closed, transition state analog (TSA) complex indicate that the enzyme undergoes substantial domain and loop rearrangements required for substrate binding, catalysis, and product release. Nuclear magnetic resonance (NMR) has shown that substrate-free arginine kinase is rigid on the ps-ns timescale (average $S^2 = 0.84 \pm 0.08$) yet quite dynamic on the μ s-ms timescale (35 residues with Rex, 12%), and that movements of the N-terminal domain and the loop comprising residues I182-G209 are rate-limiting on catalysis. Here, NMR of the TSA-bound enzyme shows similar rigidity on the ps-ns timescale (average $S^2 = 0.91 \pm 0.05$) and substantially increased μ s-ms timescale dynamics (77 residues; 22%). Many of the residues displaying μ s-ms dynamics in NMR Carr-Purcell-Meiboom-Gill (CPMG) 15N backbone relaxation dispersion experiments of the TSA complex are also dynamic in substrate-free enzyme. However, the presence of additional dynamic residues in the TSA-bound form suggests that dynamics extend through much of the C-terminal domain, which indicates that in the closed form, a larger fraction of the protein takes part in conformational transitions to the excited state(s). Conformational exchange rate constants (k_{ex}) of the TSA complex are all approximately $2500s^{-1}$, higher than any observed in the substrate-free enzyme ($800-1900s^{-1}$). Elevated μ s-ms timescale protein dynamics in the TSA-bound enzyme is more consistent with recently postulated catalytic networks involving multiple interconnected states at each step of the reaction, rather than a classical single stabilized transition state. © 2017 Elsevier Inc.

de Oliveira, D. C., Rocha, M. G., Gatti, A., Correr, A. B., Ferracane, J. L., & Sinhoret, M. A. (2015). **Effect of different photoinitiators and reducing agents on cure efficiency and color stability of resin-based composites using different LED wavelengths.** *J Dent*, 43(12), 1565-1572. doi:10.1016/j.jdent.2015.08.015

OBJECTIVES: To evaluate the effect of photoinitiators and reducing agents on cure efficiency and color stability of resin-based composites using different LED wavelengths. **METHODS:** Model resin-based composites were associated with diphenyl(2,4,6-trimethylbenzoyl) phosphine oxide (TPO), phenylbis(2,4,6-trimethylbenzoyl) phosphine oxide (BAPO) or camphorquinone (CQ) associated with 2-(dimethylamino) ethyl methacrylate (DMAEMA), ethyl 4-(dimethylamino) benzoate (EDMAB) or 4-(N,N-dimethylamino) phenethyl alcohol (DMPOH). A narrow (Smartlite, Dentisply) and a broad spectrum (Bluephase G2, Ivoclar Vivadent) LEDs were used for photo-activation ($20 J/cm^2$). Fourier transform infrared spectroscopy (FT-IR) was used to evaluate the cure efficiency for each composite, and CIELab parameters to evaluate color stability (ΔE_{00}) after aging. The UV-vis absorption spectrophotometric analysis of each photoinitiator and reducing agent was determined. Data were analyzed using two-way ANOVA and Tukey's test for multiple comparisons ($\alpha=0.05$). **RESULTS:** Higher cure efficiency was found for type-I photoinitiators photo-activated with a broad spectrum light, and for CQ-systems with a narrow band spectrum light, except when combined with an aliphatic amine (DMAEMA). Also, when combined with aromatic amines (EDMAB and DMPOH), similar cure efficiency with both wavelength LEDs was found. TPO had no cure efficiency when light-cured exclusively with a blue narrowband spectrum. CQ-systems presented higher color stability than type-I photoinitiators, especially when combined with DMPOH. **CONCLUSIONS:** After aging, CQ-based composites became more yellow and BAPO and TPO lighter and less yellow. However, CQ-systems presented higher color stability than type-I photoinitiators, as BAPO- and TPO-, despite their higher cure efficiency when photo-activated with corresponding wavelength range. **CLINICAL SIGNIFICANCE:** Color matching is initially important, but color change over time will be one of the major reasons for replacing esthetic restorations;

despite the less yellowing of these alternative photoinitiators, camphorquinone presented higher color stability.

Deng, C., Gao, C., Tian, X., Chao, B., Wang, F., Zhang, Y., . . . Liu, D. (2017). **Pharmacokinetics, tissue distribution and excretion of luteolin and its major metabolites in rats: Metabolites predominate in blood, tissues and are mainly excreted via bile.** *Journal of Functional Foods*, 35, 332-340. doi:10.1016/j.jff.2017.05.056

To elucidate the in vivo bioactivities of luteolin, an important food-derived flavonoid, its metabolic fate and pharmacokinetic properties in rats were investigated. Total of 8 metabolites were isolated from urine and bile and identified by NMR. Luteolin was firstly metabolized via either glucuronidation or methylation and could subsequently transform into methylated glucuronides. Systematic pharmacokinetic investigations demonstrated luteolin was rapidly and efficiently absorbed in rat intestine and then extensively metabolized, which was responsible of low availability of 17.5% for unchanged luteolin. Luteolin presented mainly as conjugates in systemic circulation, among which luteolin-3'-O- β -D-glucuronide was the most abundant both in plasma and most of tissues. Luteolin and its metabolites preferred to distribute in the gastrointestinal, liver, kidney and lung. Biliary excretion dominated the elimination pathways of the conjugated luteolin, especially the metabolites with 7-O-glucuronidation. The current study suggests further investigation on bioactivities of metabolites is crucial to elucidate the functional mechanism of luteolin. © 2017

Deodhar, A., & Yu, D. (2017). **Switching tumor necrosis factor inhibitors in the treatment of axial spondyloarthritis.** *Seminars in Arthritis and Rheumatism*. doi:10.1016/j.semarthrit.2017.04.005

OBJECTIVE: To assess the impact of switching tumor necrosis factor (TNF)-alpha inhibitors on patients with axial spondyloarthritis (axSpA). **METHODS:** PubMed literature searches were conducted using combinations of search terms including ankylosing spondylitis, spondyloarthropathy, spondyloarthritis, switch/switching, drug survival, and TNF/tumor necrosis factor to identify published articles with data on outcomes related to switching biologic therapies in patients with axSpA. **RESULTS:** Of the 134 studies screened, 21 were identified as reporting data on switching TNF inhibitors in patients carrying a diagnosis of axSpA or ankylosing spondylitis. The most common reasons for switching from the first TNF inhibitor were lack of efficacy (14-68%), loss of efficacy (13-61%), and adverse events/poor tolerability (13-57%). Switching TNF inhibitors was beneficial for a substantial proportion of patients with axSpA who failed to respond to initial or even second TNF inhibitor therapy and adverse effects were not enhanced. Drug survival rates were generally lower for the second (47-72% at 2 years) or third TNF inhibitor (49% at 2 years) than for the first TNF inhibitor (58-75% at 2 years). Predictors of responses in TNF-naive patients included HLA-B27 positivity, absence of enthesitis, age \leq 40 years, elevated C-reactive protein level, good functional status, and shorter disease duration. Predictors of drug survival included male sex and peripheral arthritis. Common characteristics of patients who switched TNF inhibitors included female sex, older age, more severe disease, greater symptom burden, higher erythrocyte sedimentation rate, complete ankyloses, and enthesitis. **CONCLUSION:** When the first or even the second TNF inhibitor fails, switching to an alternate one is not an unreasonable clinical therapeutic decision.

Dewland, T. A., Soliman, E. Z., Davis, B. R., Magnani, J. W., Yamal, J. M., Piller, L. B., . . . Marcus, G. M. (2016). **Effect of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) on Conduction System Disease.** *JAMA Intern Med*, 176(8), 1085-1092. doi:10.1001/jamainternmed.2016.2502

IMPORTANCE: Cardiac conduction abnormalities are associated with an increased risk for morbidity and mortality, and understanding factors that accelerate or delay conduction system disease could help to identify preventive and therapeutic strategies. Antifibrotic and anti-inflammatory properties of angiotensin-converting enzyme inhibitors and treatment for hyperlipidemia may reduce the risk for incident conduction system disease. **OBJECTIVE:** To identify the effect of pharmacologic therapy randomization and clinical risk factors on the incidence of conduction system disease. **DESIGN, SETTING, AND PARTICIPANTS:** This

secondary analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) investigation acquired data from 623 North American centers. A total of 21004 ambulatory individuals 55 years or older with hypertension and at least 1 other cardiac risk factor were included in the analysis. INTERVENTIONS: Participants were randomly assigned to receive amlodipine besylate, lisinopril, or chlorthalidone. Individuals with elevated fasting low-density lipoprotein cholesterol levels were also randomized to pravastatin sodium vs usual care. MAIN OUTCOMES AND MEASURES: An electrocardiogram (ECG) was obtained at study enrollment and every 2 years of follow-up. The development of incident first-degree atrioventricular block, left anterior fascicular block, incomplete left bundle branch block (LBBB), LBBB, incomplete right bundle branch block (RBBB), RBBB, or intraventricular conduction delay was assessed by serial ECGs. RESULTS: The 21004 participants (11758 men [56.0%]; 9246 women [44.0%]; mean [SD] age, 66.5 [7.3] years) underwent a mean (SD) follow-up of 5.0 (1.2) years. Among the 1114 participants who developed any conduction defect, 389 developed LBBB, 570 developed RBBB, and 155 developed intraventricular conduction delay. Compared with chlorthalidone, randomization to lisinopril was associated with a significant 19% reduction in conduction abnormalities (hazard ratio [HR], 0.81; 95% CI, 0.69-0.95; P = .01). Treatment with amlodipine, however, was not associated with a significant difference in conduction outcome events (HR, 0.94; 95% CI, 0.81-1.09; P = .42). Similarly, pravastatin treatment was not associated with a reduced adjusted risk for incident disease compared with usual hyperlipidemia treatment (HR, 1.13; 95% CI, 0.95-1.35; P = .18). Increased age (HR, 1.47; 95% CI, 1.34-1.63; P < .001), male sex (HR, 0.59; 95% CI, 0.50-0.73; P < .001), white race (HR, 0.59; 95% CI, 0.50-0.70; P < .001), diabetes (HR, 1.23; 95% CI, 1.07-1.42; P = .003), and left ventricular hypertrophy (HR, 3.20; 95% CI, 2.61-3.94; P < .001) were also independently associated with increased risk for conduction system disease. CONCLUSIONS AND RELEVANCE: Incident conduction system disease is significantly reduced by lisinopril therapy and is independently associated with multiple clinical factors. Further studies are warranted to determine whether pharmacologic treatment affects conduction abnormality outcomes, including pacemaker implantation. TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT00000542.

Didier, R. A., Hopkins, K. L., Coakley, F. V., Krishnaswami, S., Spiro, D. M., & Foster, B. R. (2017). **Performance characteristics of magnetic resonance imaging without contrast agents or sedation in pediatric appendicitis.** *Pediatric Radiology*. doi:10.1007/s00247-017-3897-7

BACKGROUND: Magnetic resonance imaging (MRI) has emerged as a promising modality for evaluating pediatric appendicitis. However optimal imaging protocols, including roles of contrast agents and sedation, have not been established and diagnostic criteria have not been fully evaluated. OBJECTIVE: To investigate performance characteristics of rapid MRI without contrast agents or sedation in the diagnosis of pediatric appendicitis. MATERIALS AND METHODS: We included patients ages 4-18 years with suspicion of appendicitis who underwent rapid MRI between October 2013 and March 2015 without contrast agent or sedation. After two-radiologist review, we determined performance characteristics of individual diagnostic criteria and aggregate diagnostic criteria by comparing MRI results to clinical outcomes. We used receiver operating characteristic (ROC) curves to determine cut-points for appendiceal diameter and wall thickness for optimization of predictive power, and we calculated area under the curve (AUC) as a measure of test accuracy. RESULTS: Ninety-eight MRI examinations were performed in 97 subjects. Overall, MRI had a 94% sensitivity, 95% specificity, 91% positive predictive value and 97% negative predictive value. Optimal cut-points for appendiceal diameter and wall thickness were ≥ 7 mm and ≥ 2 mm, respectively. Independently, those cut-points produced sensitivities of 91% and 84% and specificities of 84% and 43%. Presence of intraluminal fluid (30/33) or localized periappendiceal fluid (32/33) showed a significant association with acute appendicitis ($P < 0.01$), with sensitivities of 91% and 97% and specificities of 60% and 50%. For examinations in which the appendix was not identified by one or both reviewers (23/98), the clinical outcome was negative. CONCLUSION: Rapid MRI without contrast agents or sedation is accurate for diagnosis of pediatric appendicitis when multiple diagnostic criteria are considered in aggregate. Individual diagnostic criteria including optimized cut-points of ≥ 7 mm for diameter and ≥ 2 mm for wall thickness demonstrate high sensitivities but relatively low specificities. Nonvisualization of the appendix favors a negative diagnosis.

Diemer, G. S., & Stedman, K. M. (2016). **Modeling Microvirus Capsid Protein Evolution Utilizing Metagenomic Sequence Data.** *Journal of Molecular Evolution*, 83(1-2), 38-49. doi:10.1007/s00239-016-9751-y

The Microviridae are increasingly becoming recognized as one of the most globally ubiquitous and highly diverse virus families, and as such, provide an advantageous model for studying virus evolution and adaptation. Here, we utilize microvirus sequences from diverse physiochemical environments, including novel sequences from a high-temperature acidic lake, to chart the outcome of natural selection in the main structural protein of the virus. Each icosahedral microvirus virion is composed of sixty identical capsid proteins that interact along twofold, threefold and fivefold symmetry axis interfaces to encapsidate a small, circular, single-stranded DNA genome. Viable assembly of the virus is guided by scaffolding proteins, which coordinate inter-subunit contacts between the capsid proteins. Structure-based analysis indicates that amino acid sequence conservation is predominantly localized to the twofold axis interface. While preservation of this quaternary interface appears to be essential, tertiary and secondary structural features of the capsid protein are permissive to considerable sequence variation.

Dilley, S. E., Havrilesky, L. J., Bakkum-Gamez, J., Cohn, D. E., Michael Straughn, J., Caughey, A. B., & Rodriguez, M. I. (2017). **Cost-effectiveness of opportunistic salpingectomy for ovarian cancer prevention.** *Gynecologic Oncology*. doi:10.1016/j.ygyno.2017.05.034

Objectives: Data suggesting a link between the fallopian tube and ovarian cancer have led to an increase in rates of salpingectomy at the time of pelvic surgery, a practice known as opportunistic salpingectomy (OS). However, the potential benefits, risks and costs for this new practice are not well established. Our objective was to assess the cost-effectiveness of opportunistic salpingectomy at the time of laparoscopic permanent contraception or hysterectomy for benign indications. Methods: We created two models to compare the cost-effectiveness of salpingectomy versus usual care. The hypothetical study population is 50,000 women aged 45 undergoing laparoscopic hysterectomy with ovarian preservation for benign indications, and 300,000 women aged 35 undergoing laparoscopic permanent contraception. SEER data were used for probabilities of ovarian cancer cases and deaths. The ovarian cancer risk reduction, complication rates, utilities and associated costs were obtained from published literature. Sensitivity analyses and Monte Carlo simulation were performed, and incremental cost-effectiveness ratios (ICERs) were calculated to determine the cost per quality adjusted life year (QALY) gained. Results: In the laparoscopic hysterectomy cohort, OS is cost saving and would yield \$23.9 million in health care dollars saved. In the laparoscopic permanent contraception cohort, OS is cost-effective with an ICER of \$31,432/QALY compared to tubal ligation, and remains cost-effective as long as it reduces ovarian cancer risk by 54%. Monte Carlo simulation demonstrated cost-effectiveness with hysterectomy and permanent contraception in 62.3% and 55% of trials, respectively. Conclusions: Opportunistic salpingectomy for low-risk women undergoing pelvic surgery may be a cost-effective strategy for decreasing ovarian cancer risk at time of hysterectomy or permanent contraception. In our model, salpingectomy was cost-effective with both procedures, but the advantage greater at time of hysterectomy. © 2017.

Dobscha, S. K., Cromer, R., Crain, A., & Denneson, L. M. (2016). **Qualitative analysis of US Department of veterans affairs mental health clinician perspectives on patient-centered care.** *International Journal for Quality in Health Care*, 28(3), 355-362. doi:10.1093/intqhc/mzw028

OBJECTIVE: Enhanced patient involvement in care has the potential to improve patient experiences and health outcomes. As such, large national and global healthcare systems and organizations, including the US Department of Veterans Affairs (VA), have made patient-centered care a primary goal. Little is known about mental health clinician perspectives on, and experiences with, providing patient-centered care. Our main objective was to better understand VA mental health clinicians' perceptions of patient-centered care, and ascertain possible facilitators and barriers to patient-centered practices in mental health settings. DESIGN: Qualitative study of six focus groups conducted in late 2013. SETTING AND PARTICIPANTS: Thirty-five

mental health clinicians and staff from a large VA Medical Center. OUTCOMES: Transcripts were analyzed using an inductive and deductive thematic analysis approach. RESULTS: Participants described patient-centered care ideally as a process of shared discovery, and expressed general enthusiasm for patient-centered care. Participants described several ongoing patient-centered care practices but conveyed concerns about the practicalities of its full implementation. Participants expressed a strong desire to change the current biomedical culture and policies of the institution that may hinder clinicians' flexibility and clinician-clinician collaboration when serving patients. In particular, clinicians worried about being held responsible for addressing all of the needs or goals that a patient may identify. CONCLUSIONS: If patient-centered care is to be practiced fully in mental health settings, healthcare institutions need to develop multimodal strategies to enhance clinician-clinician and clinician-patient collaborations to promote and support a focus on discovery and shared accountability for outcomes.

Donahue, J. J., Santanello, A., Marsiglio, M. C., & van Male, L. M. (2017). **Acceptance and Commitment Therapy for Anger Dysregulation with Military Veterans: A Pilot Study.** *Journal of Contemporary Psychotherapy*, 1-9. doi:10.1007/s10879-017-9361-z

Anger dysregulation is a commonly reported problem by treatment-seeking military veterans that is associated with a range of negative outcomes. However, there is a paucity of studies examining interventions for anger and aggressive behavior in this population. Theory and empirical evidence suggest Acceptance and Commitment Therapy (ACT) may be a viable and effective treatment for anger dysregulation among veterans. The present study examined the feasibility and preliminary effectiveness of an open trial of an ACT group intervention for veterans reporting difficulties with anger and aggressive behavior. Twenty-three male military veterans (mean age = 54.83) initiated a 12-week ACT intervention with assessments administered at pre-treatment, post-treatment, and 6-week follow-up. Treatment completers found the intervention favorable, and participation was associated with improvements in trait physical aggression and psychological flexibility, while significant changes in anger reactivity, quality of life, and verbal aggression were not found. Results suggest group-based ACT for anger dysregulation is feasible in a male military veteran sample, and warrants further investigation. © 2017 Springer Science+Business Media New York

Dotters-Katz, S. K., Senz, K. L., Humphrey, W. M., Lee, V. R., & Caughey, A. B. (2017). **Trisomy 18 Pregnancies: Is there an Increased Maternal Risk?** *American Journal of Perinatology*. doi:10.1055/s-0037-1603679

Objective Characterize the impact of a trisomy 18 (T18) fetus on maternal and obstetric outcomes in a cohort including T18-affected deliveries. Study Design Retrospective cohort study of singleton deliveries in California from 2005 to 2008 using linked vital statistics and the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9) data to compare deliveries affected by T18 to those without known aneuploidy. Outcomes of interest included gestational diabetes mellitus (GDM), preterm delivery (PTD), preeclampsia, cesarean delivery (CD), and intrauterine fetal demise (IUFD). The χ^2 and paired t-tests were used to compare the outcomes. Multiple logistic regression was used to further characterize these risks and control potential confounders. Results Of 2,029,000 deliveries, 298 involved T18. Compared with unaffected deliveries, T18 was associated with GDM (10.7 vs. 6.5%, $p = 0.003$), PTD < 37 (40.6 vs. 9.9%, $p < 0.001$) and < 32 weeks (14.8 vs. 1.4%, $p < 0.001$), and cesarean section (56 vs. 30.2%, $p < 0.001$), but not preeclampsia. In adjusted analyses, T18 pregnancies were associated with an increased risk of PTD < 37 and < 32 weeks (adjusted odds ratio [AOR]: 5.48, 95% confidence interval [CI]: 4.29, 6.99; AOR: 10.4, 95% CI: 7.26, 14.8), and an increased odd of CD for primiparous and multiparous women (AOR: 2.41, 95% CI: 1.48, 3.91; AOR: 5.42, 95% CI: 3.90, 7.53). Risk of GDM did not persist. Conclusion Unlike trisomy 13 (T13), pregnancies complicated by fetal T18 did not appear to result in an increased risk of preeclampsia. However, there is an increased risk of a range of other obstetric complications. Copyright © 2017, Thieme Medical Publishers. All rights reserved.

Dukhovny, D. (2017). **'Does - Predict neurodevelopmental impairment in former preterm infants?' is this the right question to be asked?** *Journal of Perinatology*, 37(5), 467-468. doi:10.1038/jp.2017.19

Duncan, G. J., Plemel, J. R., Assinck, P., Manesh, S. B., Muir, F. G. W., Hirata, R., . . . Tetzlaff, W. (2017). **Myelin regulatory factor drives remyelination in multiple sclerosis.** *Acta Neuropathologica*. doi:10.1007/s00401-017-1741-7

Remyelination is limited in the majority of multiple sclerosis (MS) lesions despite the presence of oligodendrocyte precursor cells (OPCs) in most lesions. This observation has led to the view that a failure of OPCs to fully differentiate underlies remyelination failure. OPC differentiation requires intricate transcriptional regulation, which may be disrupted in chronic MS lesions. The expression of few transcription factors has been differentially compared between remyelinating lesions and lesions refractory to remyelination. In particular, the oligodendrocyte transcription factor myelin regulatory factor (MYRF) is essential for myelination during development, but its role during remyelination and expression in MS lesions is unknown. To understand the role of MYRF during remyelination, we genetically fate mapped OPCs following lyssolecithin-induced demyelination of the corpus callosum in mice and determined that MYRF is expressed in new oligodendrocytes. OPC-specific *Myrf* deletion did not alter recruitment or proliferation of these cells after demyelination, but decreased the density of new glutathione S-transferase pi positive oligodendrocytes. Subsequent remyelination in both the spinal cord and corpus callosum is highly impaired following *Myrf* deletion from OPCs. Individual OPC-derived oligodendrocytes, produced in response to demyelination, showed little capacity to express myelin proteins following *Myrf* deletion. Collectively, these data demonstrate a crucial role of MYRF in the transition of oligodendrocytes from a premyelinating to a myelinating phenotype during remyelination. In the human brain, we find that MYRF is expressed in NogoA and CNP-positive oligodendrocytes. In MS, there was both a lower density and proportion of oligodendrocyte lineage cells and NogoA+ oligodendrocytes expressing MYRF in chronically demyelinated lesions compared to remyelinated shadow plaques. The relative scarcity of oligodendrocyte lineage cells expressing MYRF in demyelinated MS lesions demonstrates, for the first time, that chronic lesions lack oligodendrocytes that express this necessary transcription factor for remyelination and supports the notion that a failure to fully differentiate underlies remyelination failure.

Duvoisin, R. M., Haley, T. L., Ren, G., Strycharska-Orczyk, I., Bonaparte, J. P., & Morgans, C. W. (2017). **Autoantibodies in Melanoma-Associated Retinopathy Recognize an Epitope Conserved Between TRPM1 and TRPM3.** *Invest Ophthalmol Vis Sci*, 58(5), 2732-2738. doi:10.1167/iovs.17-21443

Purpose: Melanoma-associated retinopathy (MAR) is a paraneoplastic syndrome associated with malignant melanoma and the presence of anti-retinal autoantibodies, including autoantibodies against transient receptor potential melanopsin 1 (TRPM1), a cation channel expressed by both melanocytes and retinal bipolar cells. The goal of this study was to further map the antigenic epitope. Methods: Patient sera were tested by immunofluorescence and Western blotting on HEK293 cells transfected with enhanced green fluorescent protein (EGFP)-TRPM1 fusion constructs and mouse retina sections. Results: The epitope recognized by MAR patient sera was mapped to a region encoded by exons 9 and 10 of the human TRPM1 gene. This region of TRPM1 is highly conserved with TRPM3, and indeed MAR sera were found to cross-react with TRPM3, a closely related channel expressed in the retinal pigment epithelium (RPE). Conclusions: These results indicate that TRPM1 autoantibodies in MAR patient sera recognize a short, intracellular segment of TRPM1. Cross-reactivity with TRPM3 in the RPE may account for other visual symptoms that are experienced by some MAR patients such as retinal and RPE detachments. We propose that TRPM1 autoantibodies are generated in response to abnormal TRPM1 polypeptides encoded by an alternate mRNA splice variant expressed by malignant melanocytes.

Eckalbar, W. L., Schlebusch, S. A., Mason, M. K., Gill, Z., Parker, A. V., Booker, B. M., . . . Ahituv, N. (2016).

Transcriptomic and epigenomic characterization of the developing bat wing. *Nat Genet*, 48(5), 528-536. doi:10.1038/ng.3537

Bats are the only mammals capable of powered flight, but little is known about the genetic determinants that shape their wings. Here we generated a genome for *Miniopterus natalensis* and performed RNA-seq and ChIP-seq (H3K27ac and H3K27me3) analyses on its developing forelimb and hindlimb autopods at sequential embryonic stages to decipher the molecular events that underlie bat wing development. Over 7,000 genes and several long noncoding RNAs, including *Tbx5-as1* and *Hottip*, were differentially expressed between forelimb and hindlimb, and across different stages. ChIP-seq analysis identified thousands of regions that are differentially modified in forelimb and hindlimb. Comparative genomics found 2,796 bat-accelerated regions within H3K27ac peaks, several of which cluster near limb-associated genes. Pathway analyses highlighted multiple ribosomal proteins and known limb patterning signaling pathways as differentially regulated and implicated increased forelimb mesenchymal condensation in differential growth. In combination, our work outlines multiple genetic components that likely contribute to bat wing formation, providing insights into this morphological innovation.

Edwards, S. T., & Landon, B. E. (2017). **Seeking Value in Healthcare: The Importance of Generalists as Primary Care Physicians.** *Journal of the American Geriatrics Society*. doi:10.1111/jgs.14937

Edwards, S. T., & Landon, B. E. (2017). **Seeking Value in Healthcare: The Importance of Generalists as Primary Care Physicians.** *J Am Geriatr Soc*. doi:10.1111/jgs.14937

Eide, C. A., & Druker, B. J. (2017). **Understanding cancer from the stem cells up.** *Nature Medicine*, 23(6), 656-657. doi:10.1038/nm.4353

A new study that uses an integrated single-cell transcriptomics approach to characterize cancer stem cell populations during treatment with molecularly targeted therapies offers insights into disease evolution and points to new therapeutic targets. © 2017 Nature America, Inc., part of Springer Nature. All rights reserved.

Ensign, C. M., & Hawkins, S. Y. (2017). **Improving Patient Self-Care and Reducing Readmissions Through an Outpatient Heart Failure Case Management Program.** *Prof Case Manag*, 22(4), 190-196. doi:10.1097/ncm.0000000000000232

Ernst, L. L., Harden, C. L., Pennell, P. B., Llewellyn, N., Lau, C., Barnard, S., . . . French, J. A. (2016). **Medication adherence in women with epilepsy who are planning pregnancy.** *Epilepsia*, 57(12), 2039-2044. doi:10.1111/epi.13586

OBJECTIVE: This study examines medication adherence among women with epilepsy via use of an electronic diary, as part of a prospective multicenter observational study designed to evaluate fertility in women with epilepsy (WWE) versus age-matched controls. **METHODS:** WWE and healthy age-matched controls, seeking pregnancy, were given an iPod Touch using a customized mobile application (the WEPOD App) for daily data tracking. Eighty-six WWE tracked seizures and antiepileptic drugs (AEDs). Tracking of nonepilepsy medications was optional. Diary data were counted from enrollment date until date of delivery, or up to 12 months if pregnancy was not achieved. Each day that subjects reported missing one or more AED was counted as nonadherence. Because adherence can only be determined in women who track consistently, we elected to include adherence data only for women who tracked >80% of days in the study. **RESULTS:**

Approximately 75% of WWE tracked >80% of days and were included in medication adherence data analysis. In this group, medication adherence rate was 97.71%; 44% of women admitted to missing an AED on at least 1 day. Among the subgroup of WWE who recorded nonepilepsy medications, AED adherence rate was 98.56%, versus 93.91% for non-AEDs. SIGNIFICANCE: The 75% compliance rate with an electronic diary suggests that it may be useful to track medication adherence in future studies and in the clinical setting. In those who tracked, the observed medication adherence rate was considerably higher than the 75% adherence rate seen in previous epilepsy studies. This might be explained in part by selection bias, but may also result from properties of the diary itself (daily reminders, real time feedback given to the provider). Women reported a higher rate of adherence to AEDs than to other prescribed medications and supplements, suggesting that perceived importance of medications likely influences medication adherence, and warrants future study.

Fazio, S., Minnier, J., Shapiro, M. D., Tsimikas, S., Tarugi, P., Aversa, M. R., . . . Tavori, H. (2017). **Threshold Effects of Circulating Angiopoietin-like 3 Levels on Plasma Lipoproteins.** *J Clin Endocrinol Metab.* doi:10.1210/jc.2016-4043

Context: Angiopoietin-like 3 (ANGPTL3) deficiency in plasma due to loss-of-function (LOF) gene mutations causes familial combined hypobetalipoproteinemia (FHBL) type 2 in homozygotes. However, the lipid phenotype in heterozygotes is much milder and does not appear to relate directly to ANGPTL3 levels. Furthermore, the low LDL phenotype in carriers of ANGPTL3 mutations is unexplained. Objective: To determine whether a reduction below a critical threshold in plasma ANGPTL3 levels is a determinant of lipoprotein metabolism in FHBL2, and to study the whether PCSK9 is involved in determining low LDL levels in this condition. Design: We studied subjects from 19 families with ANGPTL3 mutations, and subjects with FHBL type 1 due to truncated apolipoprotein B (apoB) species. Results: Total cholesterol, HDL-c, triglycerides, and HDL and LDL particle concentration correlated with plasma ANGPTL3 levels, but only when this was below 25% of normal (<60 ng/ml); (ii) VLDL particle concentration strongly correlated with plasma ANGPTL3 when this was below 58% of normal; (iii) both FHBL1 and FHBL2 subjects showed low levels of mature and LDL-bound PCSK9, and higher levels of its furin-cleaved form; and (iv) LDL-bound PCSK9 is protected from cleavage by furin, and binds to the LDL receptor more strongly compared to apoB-free PCSK9. Conclusion: Our studies suggest that the hypolipidemic effects of ANGPTL3 mutations in FHBL2 are dependent on threshold plasma ANGPTL3 levels, with differential effects on various lipoprotein particles. The increased inactivation of PCSK9 by furin in FHBL1 and FHBL2 is likely to cause increased LDL clearance and suggests novel therapeutic avenues.

Fender, E. A., Killu, A. M., Cannon, B. C., Friedman, P. A., McLeod, C. J., Hodge, D. O., . . . Cha, Y. M. (2017). **Lead extraction outcomes in patients with congenital heart disease.** *Europace: European Pacing, Arrhythmias, and Cardiac Electrophysiology*, 19(3), 441-446. doi:10.1093/europace/euw049

Aims: Patients with congenital heart disease (CHD) are at increased risk for intracardiac device malfunction and infection that may necessitate extraction; however, the risk of extraction is poorly understood. This study addresses the safety of extraction in patients with structural heart disease and previous cardiac surgery. Methods and results: This retrospective study included 40 CHD and 80 matched control patients, who underwent transvenous lead extractions between 2001 and 2014. Only leads >12 months were included. There were 77 leads in CHD patients and 146 in controls. The mean age was 38 ± 16 years in CHD patients. Ninety per cent of CHD patients had ≥ 1 cardiac surgeries when compared with 21% of controls ($P < 0.001$). The number of abandoned leads was significantly different (17 vs. 3, $P < 0.001$). Lead age was similar with an average duration of 83 ± 87 months in CHD patients and 62 ± 65 months in controls ($P = 0.24$). There was no significant difference in extraction techniques. Manual traction was successful in 40% of CHD patients and 47% of controls, and advanced techniques were used in 60 and 53% of CHD patients and controls, respectively. Complete extraction was achieved in 94% of the patients in both groups. There was no significant difference in complications. Conclusion: Lead extraction can be safely performed in patients with CHD. Despite anatomic abnormalities and longer implantation times, the difficulty of lead extraction in patients with CHD is comparable with controls. © The Author 2016.

Floeter, A. E., & McCune, J. S. (2017). **Levetiracetam for the prevention of busulfan-induced seizures in pediatric hematopoietic cell transplantation recipients.** *Journal of Oncology Pharmacy Practice, 23*(5), 344-349. doi:10.1177/1078155216651128

Objective The objective of this study was to compare clinical outcomes in children undergoing hematopoietic cell transplantation who received levetiracetam versus those who received phenytoin for the prevention of busulfan-induced seizures. **Methods** This study was an IRB-approved, single-center, retrospective analysis of pediatric patients receiving intravenous busulfan for hematopoietic cell transplantation conditioning from January 2009 to July 2014. The primary study endpoint was the incidence of seizure during busulfan administration (day -8 to 0). Key transplant related-outcomes were also collected, including the incidence of graft rejection, sinusoidal obstruction syndrome, relapse, and death. **Results** A total of 20 patients met criteria for inclusion in the study. The population was heterogeneous with regard to the indication for hematopoietic cell transplantation, donor type, stem cell source, and conditioning regimen. Nine patients (45%) received levetiracetam and 11 (55%) received phenytoin for seizure prophylaxis. No seizures or graft rejections were observed in the study population. One relapse, one case of sinusoidal obstruction syndrome, and two deaths occurred in the levetiracetam group, while no relapses, two cases of sinusoidal obstruction syndrome, and one death occurred in the phenytoin group. **Conclusion** These data suggest similar safety and effectiveness between levetiracetam and phenytoin for the prevention of busulfan-induced seizures in a small, heterogeneous pediatric hematopoietic cell transplantation population. © SAGE Publications.

Folmer, R. L., Vachhani, J. J., Theodoroff, S. M., Ellinger, R., & Riggins, A. (2017). **Auditory Processing Abilities of Parkinson's Disease Patients.** *Biomed Res Int, 2017*, 2618587. doi:10.1155/2017/2618587

Since Parkinson's Disease (PD) primarily affects older people, a majority of PD patients have age-related hearing loss (HL) that will worsen over time. The goal of this study was to assess peripheral and central auditory functions in a population of PD patients and compare the results with a group of age-matched control subjects. Study participants included 35 adults with PD (mean age = 66.9 +/- 11.2 years) and a group of 35 healthy control subjects (mean age = 65.4 +/- 12.3 years). Assessments included questionnaires, neuropsychological tests, audiometric testing, and a battery of central auditory processing tests. Both study groups exhibited patterns of sensorineural hearing loss (slightly worse in the PD group) which were typical for their age and would contribute to difficulties in communication for many participants. Compared to the control group, PD patients reported greater difficulty in hearing words people are speaking. Although 27 PD patients (77%) were good candidates for amplification, only 7 (26%) of these hearing aid candidates used the devices. Because it is important for PD patients to optimize communication with their family members, caregivers, friends, and clinicians, it is vital to identify and remediate auditory dysfunction in this population as early as possible.

Friedly, J. L., Comstock, B. A., Turner, J. A., Heagerty, P. J., Deyo, R. A., Bauer, Z., . . . Jarvik, J. G. (2016). **Long-Term Effects of Repeated Injections of Local Anesthetic With or Without Corticosteroid for Lumbar Spinal Stenosis: A Randomized Trial.** *Archives of Physical Medicine and Rehabilitation.* doi:10.1016/j.apmr.2017.02.029

Objective: To determine the overall long-term effectiveness of treatment with epidural corticosteroid injections for lumbar central spinal stenosis and the effect of repeat injections, including crossover injections, on outcomes through 12 months. **Design:** Multicenter, double-blind, randomized controlled trial comparing epidural injections of corticosteroid plus lidocaine versus lidocaine alone. **Setting:** Sixteen clinical sites. **Participants:** Participants with imaging-confirmed lumbar central spinal stenosis (N=400). **Interventions:** Participants were randomized to receive either epidural injections with corticosteroid plus lidocaine or lidocaine alone with the option of blinded crossover after 6 weeks to receive the alternate treatment. Participants could receive 1 to 2 injections from 0 to 6 weeks and up to 2 injections from 6 to 12 weeks. After 12 weeks, participants received

usual care. Main Outcome Measures: Primary outcomes were the Roland-Morris Disability Questionnaire (RDQ) (range, 0-24, where higher scores indicate greater disability) and leg pain intensity (range, 0 [no pain] to 10 [pain as bad as you can imagine]). Secondary outcomes included opioid use, spine surgery, and crossover rates. Results: At 12 months, both treatment groups maintained initial observed improvements, with no significant differences between groups on the RDQ (adjusted mean difference, -0.4; 95% confidence interval [CI], -1.6 to 0.9; $P=.55$), leg pain (adjusted mean difference, 0.1; 95% CI, -0.5 to 0.7; $P=.75$), opioid use (corticosteroid plus lidocaine: 41.4% vs lidocaine alone: 36.3%; $P=.41$), or spine surgery (corticosteroid plus lidocaine: 16.8% vs lidocaine alone: 11.8%; $P=.22$). Fewer participants randomized to corticosteroid plus lidocaine (30%, $n=60$) versus lidocaine alone (45%, $n=90$) crossed over after 6 weeks ($P=.003$). Among participants who crossed over at 6 weeks, the 6- to 12-week RDQ change did not differ between the 2 randomized treatment groups (adjusted mean difference, -1.0; 95% CI, -2.6 to 0.7; $P=.24$). In both groups, participants crossing over at 6 weeks had worse 12-month trajectories compared with participants who did not choose to crossover. Conclusions: For lumbar spinal stenosis symptoms, epidural injections of corticosteroid plus lidocaine offered no benefits from 6 weeks to 12 months beyond that of injections of lidocaine alone in terms of self-reported pain and function or reduction in use of opioids and spine surgery. In patients with improved pain and function 6 weeks after initial injection, these outcomes were maintained at 12 months. However, the trajectories of pain and function outcomes after 3 weeks did not differ by injectate type. Repeated injections of either type offered no additional long-term benefit if injections in the first 6 weeks did not improve pain. © 2016 American Congress of Rehabilitation Medicine.

Froehlich, R. J., Sandoval, G., Bailit, J. L., Grobman, W. A., Reddy, U. M., Wapner, R. J., . . . Tolosa, J. E. (2016).

Association of Recorded Estimated Fetal Weight and Cesarean Delivery in Attempted Vaginal Delivery at Term. *Obstet Gynecol*, 128(3), 487-494. doi:10.1097/aog.0000000000001571

OBJECTIVE: To evaluate the association between documentation of estimated fetal weight, and its value, with cesarean delivery. **METHODS:** This was a secondary analysis of a multicenter observational cohort of 115,502 deliveries from 2008 to 2011. Data were abstracted by trained and certified study personnel. We included women at 37 weeks of gestation or greater attempting vaginal delivery with live, nonanomalous, singleton, vertex fetuses and no history of cesarean delivery. Rates and odds ratios (ORs) were calculated for women with ultrasonography or clinical estimated fetal weight compared with women without documentation of estimated fetal weight. Further subgroup analyses were performed for estimated fetal weight categories (less than 3,500, 3,500-3,999, and 4,000 g or greater) stratified by diabetic status. Multivariable analyses were performed to adjust for important potential confounding variables. **RESULTS:** We included 64,030 women. Cesarean delivery rates were 18.5% in the ultrasound estimated fetal weight group, 13.4% in the clinical estimated fetal weight group, and 11.7% in the no documented estimated fetal weight group ($P<.001$). After adjustment (including for birth weight), the adjusted OR of cesarean delivery was 1.44 (95% confidence interval [CI] 1.31-1.58, $P<.001$) for women with ultrasound estimated fetal weight and 1.08 for clinical estimated fetal weight (95% CI 1.01-1.15, $P=.017$) compared with women with no documented estimated fetal weight (referent). The highest estimates of fetal weight conveyed the greatest odds of cesarean delivery. When ultrasound estimated fetal weight was 4,000 g or greater, the adjusted OR was 2.15 (95% CI 1.55-2.98, $P<.001$) in women without diabetes and 9.00 (95% CI 3.65-22.17, $P<.001$) in women with diabetes compared to those with estimated fetal weight less than 3,500 g. **CONCLUSION:** In this contemporary cohort of women attempting vaginal delivery at term, documentation of estimated fetal weight (obtained clinically or, particularly, by ultrasonography) was associated with increased odds of cesarean delivery. This relationship was strongest at higher fetal weight estimates, even after controlling for the effects of birth weight and other factors associated with increased cesarean delivery risk.

Funk, T., Lim, Y., Kulungowski, A. M., Prok, L., Crombleholme, T. M., Choate, K., & Bruckner, A. L. (2016). **Symptomatic Congenital Hemangioma and Congenital Hemangiomatosis Associated With a Somatic Activating Mutation in GNA11.** *JAMA Dermatol*, 152(9), 1015-1020. doi:10.1001/jamadermatol.2016.2365

IMPORTANCE: Congenital hemangiomas are uncommon benign vascular tumors that present fully formed at birth. They are rarely associated with transient hematologic abnormalities, which are typically less severe than the Kasabach-Merritt phenomenon associated with kaposiform hemangioendotheliomas. Congenital hemangiomas are typically solitary and have not been reported to occur in a multifocal, generalized pattern. **OBJECTIVE:** To describe a male infant born with an unusual, large vascular mass complicated by anemia, thrombocytopenia, and disseminated intravascular coagulopathy, as well as innumerable small vascular papules in a generalized cutaneous distribution. **DESIGN, SETTING, AND PARTICIPANT:** This case report is a descriptive observation of the results of clinical, pathologic, and genetic studies performed in a single male infant observed for 2 years (May 2013 to June 2015) for vascular anomalies at a tertiary care referral center. **MAIN OUTCOMES AND MEASURES:** Histopathologic, immunohistochemical, and genetic study results of tumor specimens and saliva. **RESULTS:** Careful pathologic study of 3 tumor specimens revealed similar lobular proliferations of bland endothelial cells. Lesional vessels did not express GLUT1 or the lymphatic marker D2-40, whereas WT1 was expressed. A somatic c.A626C, p.Q209P mutation in the GNA11 gene was identified in tumoral tissue. **CONCLUSIONS AND RELEVANCE:** These findings support a unifying diagnosis of congenital hemangioma for these vascular tumors. To date, this is the first-reported case of a hemangiomatosis presentation of congenital hemangioma. In addition to highlighting this novel phenotype, this case indicates the rare association of congenital hemangioma with hematologic abnormalities and verifies somatic activating mutations as the underlying cause of congenital hemangioma.

Garcia-Montilla, R., Imam, F., Miao, M., Stinson, K., Khan, A., & Heitner, S. (2017). **Optimal right heart filling pressure in acute respiratory distress syndrome determined by strain echocardiography.** *Echocardiography*, 34(6), 851-861. doi:10.1111/echo.13546

INTRODUCTION: Right ventricular (RV) systolic dysfunction is common in acute respiratory distress syndrome (ARDS). While preload optimization is crucial in its management, dynamic fluid responsiveness indices lack reliability, and there is no consensus on target central venous pressure (CVP). We analyzed the utility of RV free wall longitudinal strain (RVFWS) in the estimation of optimal RV filling pressure in ARDS. **METHODS:** A retrospective cross-sectional analysis of clinical data and echocardiograms of patients with ARDS was performed. Tricuspid annular plane systolic excursion (TAPSE), tricuspid peak systolic velocity (S'), RV fractional area change (RVFAC), RVFWS, CVP, systolic pulmonary artery pressure (SPAP), and left ventricular ejection fraction (LVEF) were measured. **RESULTS:** Fifty-one patients with moderate-severe ARDS were included. There were inverse correlations between CVP and TAPSE, S', RVFAC, RVFWS, and LVEF. The most significant was with RVFWS (r: .74, R2 :.55, P: .00001). Direct correlations with creatinine and lactate were noted. Receiver operating characteristic analysis showed that RVFWS -21% (normal reference value) was associated with CVP: 13 mm Hg (AUC: 0.92, 95% CI: 0.83-1.00). Regression model analysis of CVP, and RVFWS interactions established an RVFWS range from -18% to -24%. RVFWS -24% corresponded to CVP: 11 mm Hg and RVFWS -18% to CVP: 15 mm Hg. Beyond a CVP of 15 mm Hg, biventricular systolic dysfunction rapidly ensues. **CONCLUSIONS:** Our data are the first to show that an RV filling pressure of 13+/-2 mm Hg—as by CVP—correlates with optimal RV mechanics as evaluated by strain echocardiography in patients with moderate-severe ARDS.

Garster, N. C., & Henrikson, C. A. (2017). **Bedside identification of patients at risk for PVC-induced cardiomyopathy: Is ECG useful?** *Pacing and Clinical Electrophysiology*. doi:10.1111/pace.13125

BACKGROUND: Premature ventricular complexes (PVCs) are an under-recognized cause of cardiomyopathy. Standard 12-lead electrocardiogram (ECG) has potential to direct attention towards at-risk patients. **METHODS:** We performed a single center, retrospective chart review of 1,240 patients that completed ECG and Holter monitoring at Oregon Health and Science University Hospital between 01/01/2011 and 12/31/2013 to investigate the relationship of PVC frequency on ECG with burden on Holter. Primary outcome measures included PVC quantity on ECG, mean PVC quantity on Holter, and percentage of total beats on Holter recorded as PVCs. High PVC burden was defined as $\geq 10\%$ of total beats. **RESULTS:** Weighted mean percentages of total beats on Holter monitor recorded as PVCs were calculated for 0, 1, 2, and ≥ 3 PVCs

on ECG and found to be 1.4% (n = 1128), 3.5% (n = 32), 4.3% (n = 25) and 16.6% (n = 55) respectively, which represent statistically significant differences ($p < 0.001$). The positive predictive value of at least 3 PVCs on ECG for $\geq 10\%$ PVC Holter burden was 58%. Negative predictive value for 0 PVCs on ECG was 98%. The sensitivity and specificity of ECG to identify high PVC burden on Holter was 72% and 93.6% respectively when utilizing a positive ECG result as 1 PVC or more, and 44% and 98.9% respectively with ≥ 3 PVCs on ECG. The positive likelihood ratio corresponding to ≥ 3 PVCs on ECG was 40. CONCLUSION: These findings demonstrate that the number of PVCs on ECG can be utilized for quick bedside estimation of high PVC burden. This article is protected by copyright. All rights reserved.

Gatter, K. (2017). **FDA Oversight of Laboratory-Developed Tests: Where Are We Now?** *Arch Pathol Lab Med*, 141(6), 746-748. doi:10.5858/arpa.2017-0053-ED

Geerts, H., Spiros, A., Roberts, P., & Carr, R. (2016). **Towards the virtual human patient. Quantitative Systems Pharmacology in Alzheimer's disease.** *European Journal of Pharmacology*. doi:10.1016/j.ejphar.2017.05.062

Development of successful therapeutic interventions in Central Nervous Systems (CNS) disorders is a daunting challenge with a low success rate. Probable reasons include the lack of translation from preclinical animal models, the individual variability of many pathological processes converging upon the same clinical phenotype, the pharmacodynamical interaction of various comedications and last but not least the complexity of the human brain. This paper argues for a re-engineering of the pharmaceutical CNS Research & Development strategy using ideas focused on advanced computer modeling and simulation from adjacent engineering-based industries. We provide examples that such a Quantitative Systems Pharmacology approach based on computer simulation of biological processes and that combines the best of preclinical research with actual clinical outcomes can enhance translation to the clinical situation. We will expand upon (1) the need to go from Big Data to Smart Data and develop predictive and quantitative algorithms that are actionable for the pharma industry, (2) using this platform as a "knowledge machine" that captures community-wide expertise in an active hypothesis-testing approach, (3) learning from failed clinical trials and (4) the need to go beyond simple linear hypotheses and embrace complex non-linear hypotheses. We will propose a strategy for applying these concepts to the substantial individual variability of AD patient subgroups and the treatment of neuropsychiatric problems in AD. Quantitative Systems Pharmacology is a new 'humanized' tool for supporting drug discovery and development in general and CNS disorders in particular. © 2017 Elsevier B.V.

Genta, R. M., Turner, K. O., & Sonnenberg, A. (2017). **Demographic and socioeconomic influences on Helicobacter pylori gastritis and its pre-neoplastic lesions amongst US residents.** *Aliment Pharmacol Ther*. doi:10.1111/apt.14162

BACKGROUND: Gastric infection with *Helicobacter pylori* (Hp) can lead to chronic inactive gastritis, atrophy and intestinal metaplasia. **AIMS:** To investigate in a cross-sectional study these changes among different socioeconomic and ethnic groups within the USA. **METHODS:** We used the Miraca Life Sciences database, an electronic depository of clinicopathological records from patients distributed throughout the USA, to extract data from 487 587 patients who underwent oesophago-gastro-duodenoscopy with biopsy between 1/2008 and 12/2014. We then classified patients into ethnic and socioeconomic categories using previously validated algorithms, as well as ZIP code-based information derived from the 2011-2012 US Census. **RESULTS:** The prevalence of Hp increased significantly until the age-group 40-49, before it leveled off and started a gradual decrease. The prevalence of chronic inactive gastritis, atrophy, and intestinal metaplasia increased significantly with age. The prevalence of Hp, chronic inactive gastritis, intestinal metaplasia, and atrophy decreased significantly with the percentage of Whites per ZIP code. The prevalence of all four diagnoses also decreased significantly with rising levels of income or college education. Hp, chronic inactive gastritis, atrophy and intestinal metaplasia were more common among Hispanics and the influence of

income or college education less pronounced than in the entire population. Hp, chronic inactive gastritis, atrophy, and intestinal metaplasia were also more common among East-Asians, Hp and atrophy decreasing with rising income but remaining unaffected by levels of college education. CONCLUSION: Ethnicity and socioeconomic factors influence the occurrence of Hp gastritis, and its progression to chronic inactive gastritis, atrophy or intestinal metaplasia.

Gerstein, N. S., McLean, A. R., Stecker, E. C., & Schulman, P. M. (2017). **External Defibrillator Damage Associated With Attempted Synchronized Dual-Dose Cardioversion.** *Ann Emerg Med.* doi:10.1016/j.annemergmed.2017.04.005

The simultaneous use of 2 external defibrillators to administer either dual or sequential cardioversion or defibrillation for refractory cardiac arrhythmias is increasing in both the out-of-hospital and in-hospital settings. Using 2 defibrillators to administer higher energy levels than can be achieved with a single defibrillator is considered off-label and is currently not part of published advanced cardiac life support guidelines. We report the first case in which the use of dual-dose cardioversion was associated with external defibrillator damage. Because defibrillator damage, especially if undetected, jeopardizes patient safety and off-label medical product use may void the manufacturer's warranty, this case should urge users to proceed with caution when contemplating this technique.

Gobeze, R., Denard, P. J., Shishani, Y., Romeo, A. A., & Lederman, E. (2017). **Healing and functional outcome of a subscapularis peel repair with a stem-based repair after total shoulder arthroplasty.** *Journal of Shoulder and Elbow Surgery.* doi:10.1016/j.jse.2017.02.013

Background: The purpose of this study was to evaluate functional outcome and healing of a subscapularis peel with a stem-based repair after total shoulder arthroplasty (TSA). The hypothesis was that the repair would lead to subscapularis healing in the majority of cases. Methods: A prospective analysis was performed on a consecutive series of TSAs. Range of motion and functional outcome were assessed according to American Shoulder and Elbow Surgeons, Single Assessment Numeric Evaluation, Simple Shoulder Test, and visual analog scale scores at a minimum follow-up of 1 year. Belly-press and lift-off tests were also performed. An ultrasound evaluation assessed subscapularis healing at final follow-up. Results: At a mean follow-up of 15 months, 60 patients (mean age, 64 years) were examined. Mean forward flexion improved from 115° to 137°. External rotation at the side improved from 27° to 52°, and internal rotation improved from L4 to L2 (P < .05). American Shoulder and Elbow Surgeons score improved from 34.3 to 79.8 (P < .001). Likewise, the Single Assessment Numeric Evaluation and Simple Shoulder Test scores showed significant improvement from 33.1 to 85.3 and 4.3 to 10.2, respectively (P < .001). The visual analog scale score for pain decreased from 5.8 to 0.7 (P < .001). On ultrasound examination, the subscapularis was healed intact in 55 cases (91.7%), attenuated in 3 cases (5%), and torn in 2 cases (3.3%). Conclusion: A stem-based repair of a subscapularis peel after TSA leads to functional improvement in the majority of cases with >90% postoperative healing of the subscapularis. © 2017 Journal of Shoulder and Elbow Surgery Board of Trustees.

Gold, R., Bunce, A. E., Cohen, D. J., Hollombe, C., Nelson, C. A., Proctor, E. K., . . . DeVoe, J. E. (2016). **Reporting on the Strategies Needed to Implement Proven Interventions: An Example From a "Real-World" Cross-Setting Implementation Study.** *Mayo Clinic Proceedings, 91(8),* 1074-1083. doi:10.1016/j.mayocp.2016.03.014

UNLABELLED: The objective of this study was to empirically demonstrate the use of a new framework for describing the strategies used to implement quality improvement interventions and provide an example that others may follow. Implementation strategies are the specific approaches, methods, structures, and resources used to introduce and encourage uptake of a given intervention's components. Such strategies have not been regularly reported in descriptions of interventions' effectiveness, or in assessments of how proven

interventions are implemented in new settings. This lack of reporting may hinder efforts to successfully translate effective interventions into "real-world" practice. A recently published framework was designed to standardize reporting on implementation strategies in the implementation science literature. We applied this framework to describe the strategies used to implement a single intervention in its original commercial care setting, and when implemented in community health centers from September 2010 through May 2015. Per this framework, the target (clinic staff) and outcome (prescribing rates) remained the same across settings; the actor, action, temporality, and dose were adapted to fit local context. The framework proved helpful in articulating which of the implementation strategies were kept constant and which were tailored to fit diverse settings, and simplified our reporting of their effects. Researchers should consider consistently reporting this information, which could be crucial to the success or failure of implementing proven interventions effectively across diverse care settings. TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT02299791.

Goloviznina, N. A., Verghese, S. C., Yoon, Y. M., Taratula, O., Marks, D. L., & Kurre, P. (2016). **Mesenchymal Stromal Cell-derived Extracellular Vesicles Promote Myeloid-biased Multipotent Hematopoietic Progenitor Expansion via Toll-Like Receptor Engagement.** *J Biol Chem*, 291(47), 24607-24617. doi:10.1074/jbc.M116.745653

Mesenchymal stromal cells (MSCs) present in the bone marrow microenvironment secrete cytokines and angiogenic factors that support the maintenance and regenerative expansion of hematopoietic stem and progenitor cells (HSPCs). Here, we tested the hypothesis that extracellular vesicles (EVs) released by MSCs contribute to the paracrine crosstalk that shapes hematopoietic function. We systematically characterized EV release by murine stromal cells and demonstrate that MSC-derived EVs prompt a loss of HSPC quiescence with concomitant expansion of murine myeloid progenitors. Our studies reveal that HSPC expansion by MSC EVs is mediated via the MyD88 adapter protein and is partially blocked by treatment with a TLR4 inhibitor. Imaging of fluorescence protein-tagged MSC EVs corroborated their cellular co-localization with TLR4 and endosomal Rab5 compartments in HSPCs. The dissection of downstream responses to TLR4 activation reveals that the mechanism by which MSC EVs impact HSPCs involves canonical NF-kappaB signaling and downstream activation of Hif-1alpha and CCL2 target genes. Our aggregate data identify a previously unknown role for MSC-derived EVs in the regulation of hematopoiesis through innate immune mechanisms and illustrate the expansive cell-cell crosstalk in the bone marrow microenvironment.

Grassi, A., Nitri, M., Moulton, S. G., Marcheggiani Muccioli, G. M., Bondi, A., Romagnoli, M., & Zaffagnini, S. (2017). **Does the type of graft affect the outcome of revision anterior cruciate ligament reconstruction? a meta-analysis of 32 studies.** *Bone Joint J*, 99-b(6), 714-723. doi:10.1302/0301-620x.99b6.bjj-2016-0929.r2

AIMS: Our aim was to perform a meta-analysis of the outcomes of revision anterior cruciate ligament (ACL) reconstruction, comparing the use of different types of graft. MATERIALS AND METHODS: A search was performed of Medline and Pubmed using the terms "Anterior Cruciate Ligament" and "ACL" combined with "revision", "re-operation" and "failure". Only studies that reported the outcome at a minimum follow-up of two years were included. Two authors reviewed the papers, and outcomes were subdivided into autograft and allograft. Autograft was subdivided into hamstring (HS) and bone-patellar tendon-bone (BPTB). Subjective and objective outcome measures were analysed and odds ratios with confidence intervals were calculated. RESULTS: A total of 32 studies met the inclusion criteria. Five studies used HS autografts, eight reported using BPTB autografts, two used quadriceps tendon autografts and eight used various types. Seven studies reported using allografts, while the two remaining used both BPTB autografts and allografts. Overall, 1192 patients with a mean age of 28.7 years (22.5 to 39) and a mean follow-up of 5.4 years (2.0 to 9.6) were treated with autografts, while 269 patients with a mean age of 28.4 years (25 to 34.6) and a mean follow-up of 4.0 years (2.3 to 6.0) were treated with allografts. Regarding allografts, irradiation with 2.5 mrad was used in two studies while the graft was not irradiated in the seven remaining studies. Reconstructions following the use of autografts had better outcomes than those using allograft with respect to laxity, measured by KT-1000/2000 (MEDmetric Corporation) and the rates of complications and re-operations. Those following the use of allografts had better mean Lysholm and Tegner activity scores compared with autografts. If irradiated

allografts were excluded from the analysis, outcomes no longer differed between the use of autografts and allografts. Comparing the types of autograft, all outcomes were similar except for HS grafts which had better International Knee Documentation Committee scores compared with BPTB grafts. CONCLUSION: Autografts had better outcomes than allografts in revision ACL reconstruction, with lower post-operative laxity and rates of complications and re-operations. However, after excluding irradiated allografts, outcomes were similar between autografts and allografts. Overall, the choice of graft at revision ACL reconstruction should be on an individual basis considering, for instance, the preferred technique of the surgeon, whether a combined reconstruction is required, the type of graft that was previously used, whether the tunnels are enlarged and the availability of allograft. Cite this article: Bone Joint J 2017;99-B:714-23.

Graven, P. F., Meath, T. H. A., Mendelson, A., Chan, B. K. S., Dorr, D. A., & McConnell, K. J. (2016). **Preventable acute care spending for high-cost patients across payer types.** *Journal of Health Care Finance*, 42(3).

Background: Healthcare expenditures are shown to concentrate in a small percentage of individuals. Many of these expenditures are thought to be preventable. Programs have developed to target high-cost individuals with the goal of reducing cost. Two of the underlying assumptions of these programs, degree of persistence and share of preventability costs, have lacked rigorous empirical research to inform payers about the general prospects. The purpose of the study is to quantify preventable expenditures among high-cost individuals across three plan types (Medicaid, Medicare Advantage, and commercial insurance plans) in Oregon. Methods: A retrospective longitudinal analysis of claims data was conducted. Shares of acute care expenditures considered preventable were calculated for non-high cost, episodically high cost, and persistently high cost patients. The results are shown for 74,717 Medicaid, 768,865 commercially insured, and 158,503 Medicare Advantage adults from Oregon using data from 2011 to 2013 data from the State of Oregon's All Payer All Claims (APAC) database and Medicaid data from the Oregon Health Authority. Results: In 2012, high cost patients account for 61.8% of Medicaid, 69.1% of commercial, and 60.0% of Medicare Advantage inpatient expenditures. Preventable inpatient expenditures accounted for 11.8%, 4.6%, and 10.0% of inpatient spending for persistently high cost patients in Medicaid, commercial and Medicare Advantage programs. Rates of preventable ED spending for persistently high cost patients in the Medicaid, commercial, and Medicare Advantage programs were 44.7%, 38%, and 34.1% respectively. Mean reversion led to declines of 11%, 25.6%, and 30.6% in the third year of spending among persistently high cost patients in the Medicaid, commercial, and Medicare Advantage programs. Conclusions: Potentially preventable health care spending for high cost patients accounted for less than 6% of total spending. More evidence is needed to support programs that target superutilizers, as opposed to disease-conditions, as a way of reducing total health care spending.

Green, R., Wilkins, C., Thomas, S., Sekine, A., Hendrick, D. M., Voss, K., . . . Gale, M., Jr. (2017). **Oas1b-dependent immune transcriptional profiles of west nile virus infection in the collaborative cross.** *G3: Genes, Genomes, Genetics*, 7(6), 1665-1682. doi:10.1534/g3.117.041624

The oligoadenylate-synthetase (Oas) gene locus provides innate immune resistance to virus infection. In mouse models, variation in the Oas1b gene influences host susceptibility to flavivirus infection. However, the impact of Oas variation on overall innate immune programming and global gene expression among tissues and in different genetic backgrounds has not been defined. We examined how Oas1b acts in spleen and brain tissue to limit West Nile virus (WNV) susceptibility and disease across a range of genetic backgrounds. The laboratory founder strains of the mouse Collaborative Cross (CC) (A/J, C57BL/6J, 129S1/SvImJ, NOD/ShiLtJ, and NZO/HILtJ) all encode a truncated, defective Oas1b, whereas the three wild-derived inbred founder strains (CAST/EiJ, PWK/PhJ, and WSB/EiJ) encode a full-length OAS1B protein. We assessed disease profiles and transcriptional signatures of F1 hybrids derived from these founder strains. F1 hybrids included wild-type Oas1b (F/F), homozygous null Oas1b (N/N), and heterozygous offspring of both parental combinations (F/N and N/F). These mice were challenged with WNV, and brain and spleen samples were harvested for global gene expression analysis. We found that the Oas1b haplotype played a role in WNV susceptibility and disease metrics, but the presence of a functional Oas1b allele in heterozygous offspring did not absolutely

predict protection against disease. Our results indicate that Oas1b status as wild-type or truncated, and overall Oas1b gene dosage, link with novel innate immune gene signatures that impact specific biological pathways for the control of flavivirus infection and immunity through both Oas1b-dependent and independent processes. © 2017 Green et al.

Greene, J. M., Dash, P., Roy, S., McMurtrey, C., Awad, W., Reed, J. S., . . . Sacha, J. B. (2017). **MR1-restricted mucosal-associated invariant T (MAIT) cells respond to mycobacterial vaccination and infection in nonhuman primates.** *Mucosal Immunology*, 10(3), 802-813. doi:10.1038/mi.2016.91

Studies on mucosal-associated invariant T cells (MAITs) in nonhuman primates (NHP), a physiologically relevant model of human immunity, are handicapped due to a lack of macaque MAIT-specific reagents. Here we show that while MR1 ligand-contact residues are conserved between human and multiple NHP species, three T-cell receptor contact-residue mutations in NHP MR1 diminish binding of human MR1 tetramers to macaque MAITs. Construction of naturally loaded macaque MR1 tetramers facilitated identification and characterization of macaque MR1-binding ligands and MAITs, both of which mirrored their human counterparts. Using the macaque MR1 tetramer we show that NHP MAITs activated in vivo in response to both Bacillus Calmette-Guerin vaccination and Mycobacterium tuberculosis infection. These results demonstrate that NHP and human MR1 and MAITs function analogously, and establish a preclinical animal model to test MAIT-targeted vaccines and therapeutics for human infectious and autoimmune disease.

Grisch-Chan, H. M., Schlegel, A., Scherer, T., Allegri, G., Heidelberger, R., Tsikrika, P., . . . Thony, B. (2017). **Low-Dose Gene Therapy for Murine PKU Using Episomal Naked DNA Vectors Expressing PAH from Its Endogenous Liver Promoter.** *Mol Ther Nucleic Acids*, 7, 339-349. doi:10.1016/j.omtn.2017.04.013

Limited duration of transgene expression, insertional mutagenesis, and size limitations for transgene cassettes pose challenges and risk factors for many gene therapy vectors. Here, we report on physiological expression of liver phenylalanine hydroxylase (PAH) by delivery of naked DNA/minicircle (MC)-based vectors for correction of homozygous enu2 mice, a model of human phenylketonuria (PKU). Because MC vectors lack a defined size limit, we constructed a MC vector expressing a codon-optimized murine Pah cDNA that includes a truncated intron and is under the transcriptional control of a 3.6-kb native Pah promoter/enhancer sequence. This vector, delivered via hydrodynamic injection, yielded therapeutic liver PAH activity and sustained correction of blood phenylalanine comparable to viral or synthetic liver promoters. Therapeutic efficacy was seen with vector copy numbers of <1 vector genome per diploid hepatocyte genome and was achieved at a vector dose that was significantly lowered. Partial hepatectomy and subsequent liver regeneration was associated with >95% loss of vector genomes and PAH activity in liver, demonstrating that MC vectors had not integrated into the liver genome. In conclusion, MC vectors, which do not have a defined size-limitation, offer a favorable safety profile for hepatic gene therapy due to their non-integration in combination with native promoters.

Haley, K. M. (2017). **Neonatal Venous Thromboembolism.** *Front Pediatr*, 5, 136. doi:10.3389/fped.2017.00136

Neonates are the pediatric population at highest risk for development of venous thromboembolism (VTE), and the incidence of VTE in the neonatal population is increasing. This is especially true in the critically ill population. Several large studies indicate that the incidence of neonatal VTE is up almost threefold in the last two decades. Central lines, fluid fluctuations, sepsis, liver dysfunction, and inflammation contribute to the risk profile for VTE development in ill neonates. In addition, the neonatal hemostatic system is different from that of older children and adults. Platelet function, pro- and anticoagulant proteins concentrations, and fibrinolytic pathway protein concentrations are developmentally regulated and generate a hemostatic homeostasis that is unique to the neonatal time period. The clinical picture of a critically ill neonate combined with the physiologically distinct neonatal hemostatic system easily fulfills the criteria for Virchow's triad with venous stasis, hypercoagulability, and endothelial injury and puts the neonatal patient at risk for

VTE development. The presentation of a VTE in a neonate is similar to that of older children or adults and is dependent upon location of the VTE. Ultrasound is the most common diagnostic tool employed in identifying neonatal VTE, but relatively small vessels of the neonate as well as frequent low pulse pressure can make ultrasound less reliable. The diagnosis of a thrombophilic disorder in the neonatal population is unlikely to change management or outcome, and the role of thrombophilia testing in this population requires further study. Treatment of neonatal VTE is aimed at reducing VTE-associated morbidity and mortality. Recommendations for treating, though, cannot be extrapolated from guidelines for older children or adults. Neonates are at risk for bleeding complications, particularly younger neonates with more fragile intracranial vessels. Developmental alterations in the coagulation proteins as well as unique pharmacokinetics must also be taken into consideration when recommending VTE treatment. In this review, epidemiology of neonatal VTE, pathophysiology of neonatal VTE with particular attention to the developmental hemostatic system, diagnostic evaluations of neonatal VTE, and treatment guidelines for neonatal VTE will be reviewed.

Hanifin, J. M. (2017). **Adult-Onset Atopic Dermatitis: Fact or Fancy?** *Dermatologic Clinics*, 35(3), 299-302.
doi:10.1016/j.det.2017.02.009

Atopic dermatitis therapy can be a challenge in many cases. Persistence into adulthood often reflects the more severe cases and such patients have the added problems of hand eczema and thick nummular lesions that resist topical medications. Within this group are patients labeled as having adult-onset atopic dermatitis, a designation that is hard to define and probably represents those whose childhood eczema was simply forgotten. Management is difficult for most adult cases and should not be diverted by questionable labels. © 2017 Elsevier Inc.

Hasler, B. P., Franzen, P. L., de Zambotti, M., Prouty, D., Brown, S. A., Tapert, S. F., . . . Clark, D. B. (2017). **Eveningness and Later Sleep Timing Are Associated with Greater Risk for Alcohol and Marijuana Use in Adolescence: Initial Findings from the National Consortium on Alcohol and Neurodevelopment in Adolescence Study.** *Alcoholism: Clinical and Experimental Research*, 41(6), 1154-1165.
doi:10.1111/acer.13401

Background: Abundant cross-sectional evidence links eveningness (a preference for later sleep-wake timing) and increased alcohol and drug use among adolescents and young adults. However, longitudinal studies are needed to examine whether eveningness is a risk factor for subsequent alcohol and drug use, particularly during adolescence, which is marked by parallel peaks in eveningness and risk for the onset of alcohol use disorders. This study examined whether eveningness and other sleep characteristics were associated with concurrent or subsequent substance involvement in a longitudinal study of adolescents. Methods: Participants were 729 adolescents (368 females; age 12 to 21 years) in the National Consortium on Alcohol and Neurodevelopment in Adolescence study. Associations between the sleep variables (circadian preference, sleep quality, daytime sleepiness, sleep timing, and sleep duration) and 3 categorical substance variables (at-risk alcohol use, alcohol bingeing, and past-year marijuana use [y/n]) were examined using ordinal and logistic regression with baseline age, sex, race, ethnicity, socioeconomic status, and psychiatric problems as covariates. Results: At baseline, greater eveningness was associated with greater at-risk alcohol use, greater bingeing, and past-year use of marijuana. Later weekday and weekend bedtimes, but not weekday or weekend sleep duration, showed similar associations across the 3 substance outcomes at baseline. Greater baseline eveningness was also prospectively associated with greater bingeing and past-year use of marijuana at the 1-year follow-up, after covarying for baseline bingeing and marijuana use. Later baseline weekday and weekend bedtimes, and shorter baseline weekday sleep duration, were similarly associated with greater bingeing and past-year use of marijuana at the 1-year follow-up after covarying for baseline values. Conclusions: Findings suggest that eveningness and sleep timing may be under recognized risk factors and future areas of intervention for adolescent involvement in alcohol and marijuana that should be considered along with other previously identified sleep factors such as insomnia and insufficient sleep. Copyright © 2017 by the Research Society on Alcoholism

Henrikson, C. A., Sohail, M. R., Acosta, H., Johnson, E. E., Rosenthal, L., Pachulski, R., . . . Simons, G. R. (2016).

Antibacterial Envelope Is Associated With Low Infection Rates After Implantable Cardioverter-Defibrillator and Cardiac Resynchronization Therapy Device Replacement. Results of the Citadel and Centurion Studies. *JACC: Clinical Electrophysiology*. doi:10.1016/j.jacep.2017.02.016

Objective: This study sought to determine whether the nonabsorbable TYRX Antibacterial Envelope (TYRX) reduces major cardiovascular implantable electronic device (CIED) infections 12 months after implant. Background: TYRX is a monofilament polypropylene mesh impregnated with minocycline and rifampin specifically designed to hold a CIED in place and elute antimicrobials over time. There are limited data on its ability to reduce CIED infections. Methods: We prospectively enrolled patients who underwent generator replacement with an implantable cardioverter-defibrillator (ICD) or cardiac resynchronization therapy device (CRT), treated with TYRX. The primary endpoints were major CIED infection and CIED mechanical complications. Given the differences in infection rates among ICD and CRT patients, 3 different control populations were used: a published benchmark rate for ICD patients, and both site-matched and comorbidity-matched controls groups for CRT patients. Results: Overall, a major CIED infection occurred in 5 of 1,129 patients treated with TYRX (0.4%; 95% confidence interval: 0.00 to 0.90), significantly lower than the 12-month benchmark rate of 2.2% ($p = 0.0023$). Among the TYRX-treated CRT cohort, the major CIED infection rate was 0.7% compared with an infection rate of 1.0% and 1.3% ($p = 0.38$ and 0.02) in site-matched and comorbidity-matched control groups, respectively. Among the ICD group, the 12-month infection rate was 0.2% compared with the published benchmark of 2.2% ($p = 0.0052$). The most common CIED mechanical complication in study patients was pocket hematoma, which occurred in 18 of the 1,129 patients (1.6%; 95% confidence interval: 0.8 to 2.5), which is comparable with a published rate of 1.6%. Conclusions: Use of TYRX was associated with a lower major CIED infection rate. (TYRX™ Envelope for Prevention of Infection Following Replacement With a CRT or ICD; [NCT01043861/NCT01043705]). © 2017 American College of Cardiology Foundation.

Henry, J. A., McMillan, G., Dann, S., Bennett, K., Griest, S., Theodoroff, S., . . . Saunders, G. (2017). **Tinnitus management: Randomized controlled trial comparing extended-wear hearing AIDS, conventional hearing AIDS, and combination instruments.** *Journal of the American Academy of Audiology*, 28(6), 546-561. doi:10.3766/jaaa.16067

Background: Whereas hearing AIDS have long been considered effective for providing relief from tinnitus, controlled clinical studies evaluating this premise have been very limited. Purpose: The purpose of this study was to systematically determine the relative efficacy of conventional receiver-in-the-canal hearing AIDS (HA), the same hearing AIDS with a sound generator (HA1SG), and extended-wear, deep fit hearing AIDS (EWHA), to provide relief from tinnitus through a randomized controlled trial. Each of these ear-level devices was a product of Phonak, LLC. Research Design: Participants were randomized to HA, HA1SG, or EWHA and wore bilaterally fit devices for about 4 months. Fittings, adjustments, and follow-up appointments were conducted to comply with company guidelines and to ensure that all participants attended appointments on the same schedule. At 4-5 months, participants returned to complete final outcome measures, which concluded their study participation. Study Sample: Participants were 55 individuals (mean age: 63.1 years) with mild to moderately-severe hearing loss who: (a) did not currently use hearing AIDS; (b) reported tinnitus that was sufficiently bothersome to warrant intervention; and (c) were suitable candidates for each of the study devices. Data Collection and Analysis: The primary outcome measure was the Tinnitus Functional Index (TFI). Secondary outcome measures included hearing-specific questionnaires and the Quick Speech in Noise test (QuickSIN). The goal of the analysis was to evaluate efficacy of the EWHA and HA1SG devices versus the HA standard device. Results: There were 18 participants in each of the HA and EWHA groups and 19 in the HA1SG group. Gender, age, and baseline TFI severity were balanced across treatment groups. Nearly all participants had a reduction in tinnitus symptoms during the study. The average TFI change (improvement) from baseline was 21 points in the HA group, 31 points in the EWHA group, and 33 points in the HA1SG group. A "clinically significant" improvement in reaction to tinnitus (at least 13-point reduction in TFI score) was seen by 67% of HA, 82% of EWHA, and 79% of HA1SG participants. There were no statistically significant

differences in the extent to which the devices reduced TFI scores. Likewise, the hearingspecific questionnaires and QuickSIN showed improvements following use of the hearing AIDS but these improvements did not differ across device groups. Conclusions: There is insufficient evidence to conclude that any of these devices offers greater relief from tinnitus than any other one tested. However, all devices appear to offer some improvement in the functional effects of tinnitus.

Hobbs, S. J., & Nolz, J. C. (2017). **Regulation of T cell trafficking by enzymatic synthesis of O-glycans.** *Frontiers in Immunology*, 8(MAY). doi:10.3389/fimmu.2017.00600

Selectins constitute a family of oligosaccharide binding proteins that play critical roles in regulating the trafficking of leukocytes. In T cells, L-selectin (CD62L) controls the capacity for naive and memory T cells to actively survey peripheral lymph nodes, whereas P- and E-selectin capture activated T cells on inflamed vascular endothelium to initiate extravasation into non-lymphoid tissues. The capacity for T cells to interact with all of these selectins is dependent on the enzymatic synthesis of complex O-glycans, and thus, this protein modification plays an indispensable role in regulating the distribution and homing of both naive and previously activated T cells in vivo. In contrast to neutrophils, O-glycan synthesis is highly dynamic in T cell populations and is largely controlled by extracellular stimuli such as antigen recognition or signaling through cytokine receptors. Herein, we review the basic principles of enzymatic synthesis of complex O-glycans, discuss tools and reagents for studying this type of protein modification and highlight our current understanding of how O-glycan synthesis is regulated and subsequently impacts the trafficking potential of diverse T cell populations. © 2017 Hobbs and Nolz.

Hodi, F. S., Chesney, J., Pavlick, A. C., Robert, C., Grossmann, K. F., McDermott, D. F., . . . Postow, M. A. (2016).

Combined nivolumab and ipilimumab versus ipilimumab alone in patients with advanced melanoma: 2-year overall survival outcomes in a multicentre, randomised, controlled, phase 2 trial. *Lancet Oncology*, 17(11), 1558-1568. doi:10.1016/s1470-2045(16)30366-7

BACKGROUND: Results from phase 2 and 3 trials in patients with advanced melanoma have shown significant improvements in the proportion of patients achieving an objective response and prolonged progression-free survival with the combination of nivolumab (an anti-PD-1 antibody) plus ipilimumab (an anti-CTLA-4 antibody) compared with ipilimumab alone. We report 2-year overall survival data from a randomised controlled trial assessing this treatment in previously untreated advanced melanoma. **METHODS:** In this multicentre, double-blind, randomised, controlled, phase 2 trial (CheckMate 069) we recruited patients from 19 specialist cancer centres in two countries (France and the USA). Eligible patients were aged 18 years or older with previously untreated, unresectable stage III or IV melanoma and an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients were randomly assigned 2:1 to receive an intravenous infusion of nivolumab 1 mg/kg plus ipilimumab 3 mg/kg or ipilimumab 3 mg/kg plus placebo, every 3 weeks for four doses. Subsequently, patients assigned to nivolumab plus ipilimumab received nivolumab 3 mg/kg every 2 weeks until disease progression or unacceptable toxicity, whereas patients allocated to ipilimumab alone received placebo every 2 weeks during this phase. Randomisation was done via an interactive voice response system with a permuted block schedule (block size of six) and stratification by BRAF mutation status. The study funder, patients, investigators, and study site staff were masked to treatment assignment. The primary endpoint, which has been reported previously, was the proportion of patients with BRAFV600 wild-type melanoma achieving an investigator-assessed objective response. Overall survival was an exploratory endpoint and is reported in this Article. Efficacy analyses were done on the intention-to-treat population, whereas safety was assessed in all treated patients who received at least one dose of study drug. This study is registered with ClinicalTrials.gov, number NCT01927419, and is ongoing but no longer enrolling patients. **FINDINGS:** Between Sept 16, 2013, and Feb 6, 2014, we screened 179 patients and enrolled 142, randomly assigning 95 patients to nivolumab plus ipilimumab and 47 to ipilimumab alone. In each treatment group, one patient no longer met the study criteria following randomisation and thus did not receive study drug. At a median follow-up of 24.5 months (IQR 9.1-25.7), 2-year overall survival was 63.8% (95% CI 53.3-72.6) for those assigned to nivolumab plus ipilimumab and 53.6% (95% CI 38.1-66.8) for those assigned to ipilimumab

alone; median overall survival had not been reached in either group (hazard ratio 0.74, 95% CI 0.43-1.26; $p=0.26$). Treatment-related grade 3-4 adverse events were reported in 51 (54%) of 94 patients who received nivolumab plus ipilimumab compared with nine (20%) of 46 patients who received ipilimumab alone. The most common treatment-related grade 3-4 adverse events were colitis (12 [13%] of 94 patients) and increased alanine aminotransferase (ten [11%]) in the combination group and diarrhoea (five [11%] of 46 patients) and hypophysitis (two [4%]) in the ipilimumab alone group. Serious grade 3-4 treatment-related adverse events were reported in 34 (36%) of 94 patients who received nivolumab plus ipilimumab (including colitis in ten [11%] of 94 patients, and diarrhoea in five [5%]) compared with four (9%) of 46 patients who received ipilimumab alone (including diarrhoea in two [4%] of 46 patients, colitis in one [2%], and hypophysitis in one [2%]). No new types of treatment-related adverse events or treatment-related deaths occurred in this updated analysis. INTERPRETATION: Although follow-up of the patients in this study is ongoing, the results of this analysis suggest that the combination of first-line nivolumab plus ipilimumab might lead to improved outcomes compared with first-line ipilimumab alone in patients with advanced melanoma. The results suggest encouraging survival outcomes with immunotherapy in this population of patients. FUNDING: Bristol-Myers Squibb.

Holmes, M. G., Foss, E., Joseph, G., Foye, A., Beckett, B., Motamedi, D., . . . Link, T. M. (2017). **CT-Guided Bone Biopsies in Metastatic Castration-Resistant Prostate Cancer: Factors Predictive of Maximum Tumor Yield.** *Journal of Vascular and Interventional Radiology*. doi:10.1016/j.jvir.2017.04.019

PURPOSE: To evaluate the success rate of CT-guided bone biopsies in metastatic castration-resistant prostate cancer (mCRPC) and to investigate associated technical, imaging, and clinical parameters affecting diagnostic yields. **MATERIALS AND METHODS:** Eighty CT-guided bone biopsy specimens were obtained from 72 men (median age, 68 y; range, 49-89 y) enrolled in a multicenter trial to identify mechanisms of resistance in mCRPC. Successful biopsy was determined by histologic confirmation of tumor cells and successful isolation of RNA for molecular analysis. **RESULTS:** The overall success rate of CT-guided bone biopsies was 69% (55/80) based on histology and 64% (35/55) based on isolation of molecular material for RNA sequencing. Biopsies performed in lesions with areas of radiolucency had significantly higher diagnostic yields compared with lesions of predominantly dense sclerosis (95% vs 33%; $P = .002$) and lesions of predominantly subtle sclerosis (95% vs 65%; $P = .04$). Success rates increased in lesions with density ≤ 475 HU (79% for ≤ 475 HU vs 33% for > 475 HU; $P = .001$) and in lesions with ill-defined margins (76% for ill-defined margins vs 36% for well-circumscribed margins; $P = .005$). Alkaline phosphatase was the only clinical parameter to correlate significantly with diagnostic yield (83% for > 110 U/L vs 50% for ≤ 110 U/L; $P = .001$). **CONCLUSIONS:** Image-guided bone tumor biopsies can be successfully used to acquire cellular and molecular material for analyses in patients with osteoblastic prostate cancer metastases. Diagnostic yields are significantly increased in lesions with areas of radiolucency, density ≤ 475 HU, ill-defined margins, and interval growth and in patients with alkaline phosphatase > 110 U/L.

Hoorn, E. J., & Ellison, D. H. (2017). **Diuretic Resistance.** *American Journal of Kidney Diseases*, 69(1), 136-142. doi:10.1053/j.ajkd.2016.08.027

Diuretic resistance is defined as a failure to achieve the therapeutically desired reduction in edema despite a full dose of diuretic. The causes of diuretic resistance include poor adherence to drug therapy or dietary sodium restriction, pharmacokinetic issues, and compensatory increases in sodium reabsorption in nephron sites that are not blocked by the diuretic. To illustrate the pathophysiology and management of diuretic resistance, we describe a patient with nephrotic syndrome. This patient presented with generalized pitting edema and weight gain despite the use of oral loop diuretics. Nephrotic syndrome may cause mucosal edema of the intestine, limiting the absorption of diuretics. In addition, the patient's kidney function had deteriorated, impairing the tubular secretion of diuretics. He was admitted for intravenous loop diuretic treatment. However, this was ineffective, likely due to compensatory sodium reabsorption by other tubular segments. The combination of loop diuretics with triamterene, a blocker of the epithelial sodium channel, effectively reduced body weight and edema. Recent data suggest that plasmin in nephrotic urine can activate the

epithelial sodium channel, potentially contributing to the diuretic resistance in this patient. This case is used to illustrate and review the mechanisms of, and possible interventions for, diuretic resistance.

Hopkins, A. M., White, K. P., & Simpson, E. L. (2017). **Isoradiotopic response of lichen planus after radiotherapy of the breast.** *JAAD Case Rep*, 3(3), 246-249. doi:10.1016/j.jdcr.2017.02.023

Hourston, S., & Atchley, R. (2017). **Autism and Mind-Body Therapies: A Systematic Review.** *Journal of Alternative and Complementary Medicine*, 23(5), 331-339. doi:10.1089/acm.2016.0336

Background: Mind-body therapies are often used by people with autism spectrum disorders (ASD). However, there has been little examination into which types of mind-body therapies have been investigated for people with ASD and for what purposes. A systematic review was conducted to evaluate the existing evidence for mind-body therapies for people with ASD, particularly to determine the types of mind-body therapies used and the outcomes that are targeted. Methods: PubMed, PsychInfo, and Scopus were searched using terms for ASD and mind-body therapies. Sixteen studies were selected for review; these studies tested interventions using mindfulness, meditation, yoga, Nei Yang Gong, and acceptance commitment therapy. Most study outcomes targeted behavior, psychological symptoms, and quality of life for children and adults with ASD as well as their parents. Results: There was little overlap between studies on the types of mind-body therapies used and associated outcomes, and only three of the studies were randomized controlled trials. Most studies were small and uncontrolled. Some studies modified the mind-body therapies to increase accessibility for people with ASD. Conclusion: The evidence for mind-body therapies for people with ASD is limited and would benefit from larger randomized controlled trials. © Copyright 2017, Mary Ann Liebert, Inc. 2017.

Hurtado, D. A., Kim, S. S., Subramanian, S. V., Dennerlein, J. T., Christiani, D. C., Hashimoto, D. M., & Sorensen, G. (2017). **Nurses' but not supervisors' safety practices are linked with job satisfaction.** *Journal of Nursing Management*. doi:10.1111/jonm.12484

AIMS: To test the associations of safety practices as reported by nurses and their respective unit supervisors with job satisfaction. BACKGROUND: Psychosocial workplace factors are associated with job satisfaction; however, it is unknown whether nurses and supervisors accounts of safety practices are differentially linked to this outcome. METHODS: Cross-sectional study design including nurses (n = 1052) nested in 94 units in two hospitals in Boston (MA, USA). Safety practices refer to the identification and control of occupational hazards at the unit. Safety practices were measured aggregating nurses' responses per unit, and supervisory levels. Individual's job satisfaction for each nurse was the response variable. RESULTS: Supervisors assessed safety practices more favourably than their unit nursing staff. Adjusted random intercept logistic regressions showed that the odds of higher job satisfaction were higher for nurses at units with better safety practices (OR: 1.67, 95% CI: 1.04, 2.68) compared with nurses at units that averaged lower safety practices. Supervisors' reports of safety practices were not correlated with the job satisfaction of their staff. CONCLUSIONS: Adequate safety practices might be a relevant managerial role that enhances job satisfaction among nurses. IMPLICATIONS FOR NURSING MANAGEMENT: Nursing supervisors should calibrate their safety assessments with their nursing staff to improve nurses' job satisfaction.

Hyun, H. K., Christoferson, C. K., Pfeifer, C. S., Felix, C., & Ferracane, J. L. (2017). **Effect of shade, opacity and layer thickness on light transmission through a nano-hybrid dental composite during curing.** *J Esthet Restor Dent*. doi:10.1111/jerd.12311

OBJECTIVE: The aim of this study was to investigate the effect of shade and opacity on the change in light transmission through different thicknesses of a nano-hybrid composite during curing. MATERIALS AND METHODS: Twelve different shades of Venus Diamond (Heraeus Kulzer) were placed in disk shaped molds

with thickness of 1, 2, and 3 mm (n = 3 per group) and cured with an LED light-curing unit. Initial, final and average irradiance, and the total amount of energy passing through the specimen were measured using the MARC Resin Calibrator at every 10s for a total of 40s. The translucency parameter and the contrast ratio were obtained using a chromameter. Results were analyzed with ANOVA/Tukey's test (alpha = 0.05). RESULTS: All shades and all thicknesses (up to 3 mm) experienced an increase in light transmittance during curing. The majority of the increase occurred during the initial 10s exposure, with significant increase occurring from subsequent exposures only in thicker specimens (i.e., 3 mm). The increase in irradiance at the bottom during curing was dependent on shade, with darker shades and greater depths of material showing less increase. CONCLUSIONS: For one specific resin composite formulation, an increase in translucency occurs as cure progresses, and the increase is enhanced for composites with greater lightness and lower contrast ratio. CLINICAL SIGNIFICANCE: Composites demonstrate increased light transmittance as curing progress, which may improve depth of cure. The thicker composite showed the least increase in light transmission within the same shade. The increase in translucency is enhanced for composites with great lightness and lower contrast ratio.

Ilie, N., Hilton, T. J., Heintze, S. D., Hickel, R., Watts, D. C., Silikas, N., . . . Ferracane, J. L. (2017). **Academy of Dental Materials guidance-Resin composites: Part I-Mechanical properties.** *Dental Materials*. doi:10.1016/j.dental.2017.04.013

Objective: The objective of this project, which was initiated from the Academy of Dental Materials, was to review and critically appraise methods to determine fracture, deformation and wear resistance of dental resin composites, in an attempt to provide guidance for investigators endeavoring to study these properties for these materials. Methods: Test methods have been ranked in the priority of the specific property being tested, as well as of the specific test methods for evaluating that property. Focus was placed on the tests that are considered to be of the highest priority in terms of being the most useful, applicable, supported by the literature, and which show a correlation with clinical findings. Others are mentioned briefly for the purpose of being inclusive. When a standard test method exists, including those used in other fields, these have been identified in the beginning of each section. Also, some examples from the resin composite literature are included for each test method. Results: The properties for evaluating resin composites were ranked in the priority of measurement as following: (1) Strength, Elastic Modulus, Fracture toughness, Fatigue, Indentation Hardness, Wear-abrasion (third body) and Wear-attribution (contact/two body), (2) Toughness, Edge strength (chipping) and (3) Wear determined by toothbrush. Significance: The following guidance is meant to aid the researcher in choosing the proper method to assess key properties of dental resin composites with regard to their fracture, deformation and wear resistance. © 2017 The Academy of Dental Materials.

Ioannou, G. N., Beste, L. A., Chang, M. F., Green, P. K., Lowy, E., Tsui, J. I., . . . Berry, K. (2016). **Effectiveness of Sofosbuvir, Ledipasvir/Sofosbuvir, or Paritaprevir/Ritonavir/Ombitasvir and Dasabuvir Regimens for Treatment of Patients With Hepatitis C in the Veterans Affairs National Health Care System.** *Gastroenterology*, 151(3), 457-471.e455. doi:10.1053/j.gastro.2016.05.049

BACKGROUND & AIMS: We investigated the real-world effectiveness of sofosbuvir, ledipasvir/sofosbuvir, and paritaprevir/ritonavir/ombitasvir and dasabuvir (PrOD) in treatment of different subgroups of patients infected with hepatitis C virus (HCV) genotypes 1, 2, 3, or 4. METHODS: We performed a retrospective analysis of data from 17,487 patients with HCV infection (13,974 with HCV genotype 1; 2131 with genotype 2; 1237 with genotype 3; and 135 with genotype 4) who began treatment with sofosbuvir (n = 2986), ledipasvir/sofosbuvir (n = 11,327), or PrOD (n = 3174), with or without ribavirin, from January 1, 2014 through June 20, 2015 in the Veterans Affairs health care system. Data through April 15, 2016 were analyzed to assess completion of treatments and sustained virologic response 12 weeks after treatment (SVR12). Mean age of patients was 61 +/- 7 years, 97% were male, 52% were non-Hispanic white, 29% were non-Hispanic black, 32% had a diagnosis of cirrhosis (9.9% with decompensated cirrhosis), 36% had a Fibrosis-4 index score >3.25 (indicator of cirrhosis), and 29% had received prior antiviral treatment. RESULTS: An SVR12 was achieved by 92.8% (95% confidence interval [CI], 92.3%-93.2%) of subjects with HCV genotype 1

infection (no significant difference between ledipasvir/sofosbuvir and PrOD regimens), 86.2% (95% CI, 84.6%-87.7%) of those with genotype 2 infection (treated with sofosbuvir and ribavirin), 74.8% (95% CI, 72.2%-77.3%) of those with genotype 3 infection (77.9% in patients given ledipasvir/sofosbuvir plus ribavirin, 87.0% in patients given sofosbuvir and pegylated-interferon plus ribavirin, and 70.6% of patients given sofosbuvir plus ribavirin), and 89.6% (95% CI 82.8%-93.9%) of those with genotype 4 infection. Among patients with cirrhosis, 90.6% of patients with HCV genotype 1, 77.3% with HCV genotype 2, 65.7% with HCV genotype 3, and 83.9% with HCV genotype 4 achieved an SVR12. Among previously treated patients, 92.6% with genotype 1; 80.2% with genotype 2; 69.2% with genotype 3; and 93.5% with genotype 4 achieved SVR12. Among treatment-naïve patients, 92.8% with genotype 1; 88.0% with genotype 2; 77.5% with genotype 3; and 88.3% with genotype 4 achieved SVR12. Eight-week regimens of ledipasvir/sofosbuvir produced an SVR12 in 94.3% of eligible patients with HCV genotype 1 infection; this regimen was underused. CONCLUSIONS: High proportions of patients with HCV infections genotypes 1-4 (ranging from 75% to 93%) in the Veterans Affairs national health care system achieved SVR12, approaching the results reported in clinical trials, especially in patients with genotype 1 infection. An 8-week regimen of ledipasvir/sofosbuvir is effective for eligible patients with HCV genotype 1 infection and could reduce costs. There is substantial room for improvement in SVRs among persons with cirrhosis and genotype 2 or 3 infections.

Irwin, D. J., Grossman, M., Weintraub, D., Hurtig, H. I., Duda, J. E., Xie, S. X., . . . Trojanowski, J. Q. (2017).

Neuropathological and genetic correlates of survival and dementia onset in synucleinopathies: a retrospective analysis. *Lancet Neurol*, 16(1), 55-65. doi:10.1016/s1474-4422(16)30291-5

BACKGROUND: Great heterogeneity exists in survival and the interval between onset of motor symptoms and dementia symptoms across synucleinopathies. We aimed to identify genetic and pathological markers that have the strongest association with these features of clinical heterogeneity in synucleinopathies. METHODS: In this retrospective study, we examined symptom onset, and genetic and neuropathological data from a cohort of patients with Lewy body disorders with autopsy-confirmed alpha synucleinopathy (as of Oct 1, 2015) who were previously included in other studies from five academic institutions in five cities in the USA. We used histopathology techniques and markers to assess the burden of tau neurofibrillary tangles, neuritic plaques, alpha-synuclein inclusions, and other pathological changes in cortical regions. These samples were graded on an ordinal scale and genotyped for variants associated with synucleinopathies. We assessed the interval from onset of motor symptoms to onset of dementia, and overall survival in groups with varying levels of comorbid Alzheimer's disease pathology according to US National Institute on Aging-Alzheimer's Association neuropathological criteria, and used multivariate regression to control for age at death and sex. FINDINGS: On the basis of data from 213 patients who had been followed up to autopsy and met inclusion criteria of Lewy body disorder with autopsy-confirmed alpha synucleinopathy, we identified 49 (23%) patients with no Alzheimer's disease neuropathology, 56 (26%) with low-level Alzheimer's disease neuropathology, 45 (21%) with intermediate-level Alzheimer's disease neuropathology, and 63 (30%) with high-level Alzheimer's disease neuropathology. As levels of Alzheimer's disease neuropathology increased, cerebral alpha-synuclein scores were higher, and the interval between onset of motor and dementia symptoms and disease duration was shorter ($p < 0.0001$ for all comparisons). Multivariate regression showed independent negative associations of cerebral tau neurofibrillary tangles score with the interval between onset of motor and dementia symptoms (beta -4.0, 95% CI -5.5 to -2.6; $p < 0.0001$; R^2 0.22, $p < 0.0001$) and with survival (-2.0, -3.2 to -0.8; 0.003; 0.15, < 0.0001) in models that included age at death, sex, cerebral neuritic plaque scores, cerebral alpha-synuclein scores, presence of cerebrovascular disease, MAPT haplotype, and APOE genotype as covariates. INTERPRETATION: Alzheimer's disease neuropathology is common in synucleinopathies and confers a worse prognosis for each increasing level of neuropathological change. Cerebral neurofibrillary tangles burden, in addition to alpha-synuclein pathology and amyloid plaque pathology, are the strongest pathological predictors of a shorter interval between onset of motor and dementia symptoms and survival. Diagnostic criteria based on reliable biomarkers for Alzheimer's disease neuropathology in synucleinopathies should help to identify the most appropriate patients for clinical trials of emerging therapies targeting tau, amyloid-beta or alpha synuclein, and to stratify them by level of

Alzheimer's disease neuropathology. FUNDING: US National Institutes of Health (National Institute on Aging and National Institute of Neurological Disorders and Stroke).

Ishikawa, Y., Mizuno, K., & Bächinger, H. P. (2017). **Ziploc-ing the structure 2.0: Endoplasmic reticulum-resident peptidyl prolyl isomerases show different activities toward hydroxyproline.** *Journal of Biological Chemistry*, 292(22), 9273-9282. doi:10.1074/jbc.M116.772657

Extracellular matrix proteins are biosynthesized in the rough endoplasmic reticulum (rER), and the triple-helical protein collagen is the most abundant extracellular matrix component in the human body. Many enzymes, molecular chaperones, and post-Translational modifiers facilitate collagen biosynthesis. Collagen contains a large number of proline residues, so the cis/trans isomerization of proline peptide bonds is the rate-limiting step during triple-helix formation. Accordingly, the rERresident peptidyl prolyl cis/trans isomerases (PPIases) play an important role in the zipper-like triple-helix formation in collagen. We previously described this process as "Ziploc-ing the structure" and now provide additional information on the activity of individual rER PPIases. We investigated the substrate preferences of these PPIases in vitro using type III collagen, the unhydroxylated quarter fragment of type III collagen, and synthetic peptides as substrates. We observed changes in activity of six rER-resident PPIases, cyclophilin B (encoded by the PPIB gene), FKBP13 (FKBP2), FKBP19 (FKBP11), FKBP22 (FKBP14), FKBP23 (FKBP7), and FKBP65 (FKBP10), due to posttranslational modifications of proline residues in the substrate. Cyclophilin B and FKBP13 exhibited much lower activity toward post-Translationally modified substrates. In contrast, FKBP19, FKBP22, and FKBP65 showed increased activity toward hydroxyproline-containing peptide substrates. Moreover, FKBP22 showed a hydroxyproline-dependent effect by increasing the amount of refolded type III collagen in vitro and FKBP19 seems to interact with triple helical type I collagen. Therefore, we propose that hydroxyproline modulates the rate of Ziploc-ing of the triple helix of collagen in the rER. © 2017 by The American Society for Biochemistry and Molecular Biology, Inc.

Ivanov, I., Shakhawat, R., Sun, M. F., Dickeson, S. K., Puy, C., McCarty, O. J. T., . . . Gailani, D. (2017). **Nucleic acids as cofactors for factor XI and prekallikrein activation: Different roles for high-molecular-weight kininogen.** *Thrombosis and Haemostasis*, 117(4), 671-681. doi:10.1160/TH16-09-0691

The plasma zymogens factor XI (fXI) and prekallikrein (PK) are activated by factor XIIa (fXIIa) during contact activation. Polyanions such as DNA and RNA may contribute to thrombosis and inflammation partly by enhancing PK and fXI activation. We examined PK and fXI activation in the presence of nucleic acids, and determine the effects of the cofactor high molecular weight kininogen (HK) on the reactions. In the absence of HK, DNA and RNA induced fXI autoactivation. Proteases known to activate fXI (fXIIa and thrombin) did not enhance this process appreciably. Nucleic acids had little effect on PK activation by fXIIa in the absence of HK. HK had significant but opposite effects on PK and fXI activation. HK enhanced fXIIa activation of PK in the presence of nucleic acids, but blocked fXI autoactivation. Thrombin and fXIIa could overcome the HK inhibitory effect on autoactivation, indicating these proteases are necessary for nucleic acid-induced fXI activation in an HK-rich environment such as plasma. In contrast to PK, which requires HK for optimal activation, fXI activation in the presence of nucleic acids depends on anion binding sites on the fXI molecule. The corresponding sites on PK are not necessary for PK activation. Our results indicate that HK functions as a cofactor for PK activation in the presence of nucleic acids in a manner consistent with classic models of contact activation. However, HK has, on balance, an inhibitory effect on nucleic acid-supported fXI activation and may function as a negative regulator of fXI activation. © Schattauer 2017

Jain, A., Lafage, V., Kelly, M. P., Hassanzadeh, H., Neuman, B. J., Sciubba, D. M., . . . Kebaish, K. M. (2016). **Validity, Reliability, and Responsiveness of SRS-7 as an Outcomes Assessment Instrument for Operatively Treated Patients With Adult Spinal Deformity.** *Spine (Phila Pa 1976)*, 41(18), 1463-1468. doi:10.1097/brs.0000000000001540

STUDY DESIGN: A retrospective analysis. OBJECTIVE: The aim of our study was to compare the normality, concurrent validity, internal consistency, responsiveness, and dimensionality of an item response theory-derived seven-question instrument (SRS-7), against the Scoliosis Research Society-22r (SRS-22r) questionnaire in operatively treated patients with adult spinal deformity (ASD). SUMMARY OF BACKGROUND DATA: Compared with SRS-22r, SRS-7 (which has been validated in operatively treated patients with adolescent idiopathic scoliosis) has advantages of being short, unidimensional, and linear. METHODS: A prospective database of ASD patients was queried for patients 18 years or older who were operatively treated, and who answered pre- and postoperative (at 2-year follow-up) SRS-22r questions (n = 276). Corresponding SRS-7 scores were calculated using answers to SRS-22r items 1, 4, 6, 10, 18, 19, and 20. Significance was set at a P value less than 0.01. RESULTS: SRS-7 and SRS-22r were normally distributed preoperatively but not postoperatively. SRS-7 and SRS-22r scores had high correlation both preoperatively ($r = 0.76$, $P < 0.01$) and postoperatively ($r = 0.83$, $P < 0.01$). The internal consistency reliability Cronbach alpha values were 0.61 (SRS-7) and 0.83 (SRS-22r) preoperatively and 0.91 (SRS-7) and 0.95 (SRS-22r) postoperatively. SRS-7 was found to be more responsive than SRS-22r with measures of effect size: Cohen $d = 1.21$ versus 1.13, Hedge $g = 1.21$ versus 1.13, and effect size correlation $r = 0.52$ versus 0.49. Iterative principal factor analysis of pre- and postoperative scores showed the presence of one dominant latent factor in SRS-7 (unidimensionality) and four latent factors in SRS-22r (multidimensionality). CONCLUSION: SRS-7 is a valid, reliable, responsive, and unidimensional instrument, which can be used as a short-form alternative to the SRS-22r for assessing global changes in patient-reported outcomes over time in patients with ASD. LEVEL OF EVIDENCE: 3.

Jayaram, H., Phillips, J. I., Lozano, D. C., Choe, T. E., Cepurna, W. O., Johnson, E. C., . . . Keller, K. E. (2017). **Comparison of microRNA expression in aqueous humor of normal and primary open-angle glaucoma patients using PCR arrays: A pilot study.** *Investigative Ophthalmology and Visual Science*, 58(7), 2884-2890. doi:10.1167/iovs.17-21844

PURPOSE. MicroRNAs (miRNAs) are small, endogenous noncoding RNAs that have been detected in human aqueous humor (AH). Prior studies have pooled samples to obtain sufficient quantities for analysis or used next-generation sequencing. Here, we used PCR arrays with preamplification to identify and compare miRNAs from individual AH samples between patients with primary open-angle glaucoma (POAG) and normal controls. METHODS. AH was collected before cataract surgery from six stable, medically treated POAG patients and eight age-matched controls. Following reverse transcription and preamplification, individual patient samples were profiled on Taqman Low Density MicroRNA Array Cards. Differentially expressed miRNAs were stratified for fold changes larger than ± 2 and for significance of $P < 0.05$. Significant Kyoto Encyclopedia of Genes and Genomes pathways influenced by the differentially expressed miRNAs were identified using the predicted target module of the miRWalk 2.0 database. RESULTS. This approach detected 181 discrete miRNAs, which were consistently expressed across all samples of both experimental groups. Significant up-regulation of miR-518d and miR-143, and significant down-regulation of miR-660, was observed in the AH of POAG patients compared with controls. These miRNAs were predicted to reduce cell proliferation and extracellular matrix remodeling, endocytosis, Wnt signaling, ubiquitin-mediated proteolysis, and adherens junction function. CONCLUSIONS. This pilot study demonstrates that miRNA expression within the AH of POAG patients differs from age-matched controls. AH miRNAs exhibit potential as biomarkers of POAG, which merits further investigation in a larger case-controlled study. This technique provides a cost-effective and sensitive approach to assay miRNAs in individual patient samples without the need for pooling. © 2017 The Authors.

Jewell, M. L. (2017). **Letter to the PRS Editor: "Comparing Round and Anatomically Shaped Implants in Augmentation Mammoplasty: The Experts' Ability to Differentiate the Type of Implant"**. *Plast Reconstr Surg*. doi:10.1097/prs.00000000000003734

Johnson, D. A., Lieberman, D., Inadomi, J. M., Ladabaum, U., Becker, R. C., Gross, S. A., . . . Robertson, D. J. (2017). **Increased Post-procedural Non-gastrointestinal Adverse Events After Outpatient Colonoscopy in High-risk Patients.** *Clinical Gastroenterology and Hepatology*, 15(6), 883-891.e889. doi:10.1016/j.cgh.2016.12.015

Background & Aims The incidence and predictors of non-gastrointestinal (GI) adverse events (AEs) after colonoscopy are not well-understood. We studied the effects of antithrombotic agents, cardiopulmonary comorbidities, and age on risk of non-GI AEs after colonoscopy. **Methods** We performed a retrospective longitudinal analysis to assess the diagnosis, procedure, and prescription drug codes in a United States commercial claims database (March 2010–March 2012). Data from patients at increased risk (n = 82,025; defined as patients with pulmonary comorbidities or cardiovascular disease requiring antithrombotic medications) were compared with data from 398,663 average-risk patients. In a 1:1 matched analysis, 51,932 patients at increased risk, examined by colonoscopy, were compared with 51,932 matched (on the basis of age, sex, and comorbidities) patients at increased risk who did not undergo colonoscopy. We tracked cardiac, pulmonary, and neurovascular events 1–30 days after colonoscopy. **Results** Thirty days after outpatient colonoscopy, non-GI AEs were significantly higher in patients taking antithrombotic medications (7.3%; odds ratio [OR], 10.75; 95% confidence interval, 10.13–11.42) or those with pulmonary comorbidities (1.8%; OR, 2.44; 95% confidence interval, 2.27–2.62) vs average-risk patients (0.7%) and in patients 60–69 years old (OR, 2.21; 95% confidence interval, 2.01–2.42) or 70 years or older (OR, 6.45; 95% confidence interval, 5.89–7.06), compared with patients younger than 50 years. The 30-day incidence of non-GI AEs in patients at increased risk who underwent colonoscopy was also significantly higher than in matched patients at increased risk who did not undergo colonoscopy in the anticoagulant group (OR, 2.31; 95% confidence interval, 2.01–2.65) and in the chronic obstructive pulmonary disease group (OR, 1.33; 95% confidence interval, 1.13–1.56). **Conclusions** Increased number of comorbidities and older age (older than 60 years) are associated with increased risk of non-GI AEs after colonoscopy. These findings indicate the importance of determining comorbid risk and evaluating antithrombotic management before colonoscopy. © 2017 AGA Institute

Kahan, S., Cuker, A., Kushner, R. F., Maahs, J., Recht, M., Wadden, T., . . . Cooper, D. (2017). **Prevalence and impact of obesity in people with haemophilia: Review of literature and expert discussion around implementing weight management guidelines.** *Haemophilia*. doi:10.1111/hae.13291

Obesity affects more than 35% of Americans, increasing the risk of more than 200 comorbid conditions, impaired quality of life and premature mortality. This review aimed to summarize literature published over the past 15 years regarding the prevalence and impact of obesity in people with haemophilia (PWH) and to discuss implementing general guidelines for weight management in the context of the haemophilia comprehensive care team. Although few studies have assessed the effects of obesity on haemophilia-specific outcomes, existing evidence indicates an important impact of weight status on lower extremity joint range of motion and functional disability, with potentially important effects on overall quality of life. Data regarding bleeding tendency in PWH with coexisting obesity are largely inconclusive; however, some individuals may experience reduced joint bleeds following moderate weight loss. Additionally, conventional weight-based dosing of factor replacement therapy leads to increased treatment costs for PWH with obesity or overweight, suggesting pharmacoeconomic benefits of weight loss. Evidence-based recommendations for weight loss include behavioural strategies to reduce caloric intake and increase physical activity, pharmacotherapy and surgical therapy in appropriate patients. Unique considerations in PWH include bleed-related risks with physical activity; thus, healthcare professionals should advise patients on types and intensities of, and approaches to, physical activity, how to adjust treatment to accommodate exercise and how to manage potential activity-related bleeding. Increasing awareness of these issues may improve identification of PWH with coexisting obesity and referral to appropriate specialists, with potentially wide-ranging benefits in overall health and well-being.

Kaneshiro, B., Tschann, M., Jensen, J., Bednarek, P., Texeira, R., & Edelman, A. (2016). **Blood loss at the time of surgical abortion up to 14 weeks in anticoagulated patients: A case series.** *Contraception*. doi:10.1016/j.contraception.2017.03.003

Objective: To describe estimated blood loss (EBL) with surgical abortion ≤ 14 weeks' gestation in anticoagulated patients. Study design: We invited 170 clinicians involved in a professional listserv to report cases when they performed a surgical abortion on a patient ≤ 14 weeks' gestation taking an anticoagulant. Clinicians reported EBL and bleeding-related complications (need for a blood transfusion, additional surgical procedures to treat bleeding). We contacted clinicians 30 days postprocedure to capture postoperative complications. Results: Clinicians reported 52 cases between February 2011 and October 2013. Thirty percent of patients (16/52) stopped the anticoagulant with adequate time for the effects to abate prior to surgery (6 h for heparin, 24 h for low-molecular-weight heparin, International Normalized Ratio ≤ 1.7 the day prior to surgery for warfarin), while 69% (36/52) continued the anticoagulant either at therapeutic (25/36) or subtherapeutic (16/36) doses. Seventy-eight percent (28/36) of patients who continued the anticoagulant had an EBL of 50 mL or less compared to 88% (14/16) of those who stopped the anticoagulant with adequate time for its effects to abate ($p=.73$). Bleeding-related complications occurred in four anticoagulated patients and none of the patients who discontinued anticoagulant therapy. Conclusion: Continuation of anticoagulation for planned surgical abortion under 84 days does not appear to be associated with heavy bleeding. © 2017 Elsevier Inc.

Kay, J., & Winthrop, K. L. (2017). **Pharmacotherapy: Biosimilar switching - "To set a form upon desired change".** *Nature Reviews: Rheumatology*, 13(7), 391-392. doi:10.1038/nrrheum.2017.79

Keiser, T. L., & Purdy, G. E. (2017). **Killing Mycobacterium tuberculosis in vitro: What model systems can teach us.** *Microbiology Spectrum*, 5(3). doi:10.1128/microbiolspec.TBTB2-0028-2016

Tuberculosis is one of the most successful human diseases in our history due in large part to the multitude of virulence factors exhibited by the causative agent, Mycobacterium tuberculosis. Understanding the pathogenic nuances of this organism in the context of its human host is an ongoing topic of study facilitated by isolating cells from model organisms such as mice and non-human primates. However, M. tuberculosis is an obligate intracellular human pathogen, and disease progression and outcome in these model systems can differ from that of human disease. Current in vitro models of infection include primary macrophages and macrophage-like immortalized cell lines as well as the induced pluripotent stem cell-derived cell types. This article will discuss these in vitro model systems in general, what we have learned so far about utilizing them to answer questions about pathogenesis, the potential role of other cell types in innate control of M. tuberculosis infection, and the development of new coculture systems with multiple cell types. As we continue to expand current in vitro systems and institute new ones, the knowledge gained will improve our understanding of not only tuberculosis but all infectious diseases. © 2017 American Society for Microbiology. All rights reserved.

Khan, K. N., El-Asrag, M. E., Ku, C. A., Holder, G. E., McKibbin, M., Arno, G., . . . Consortium, U. K. I. R. D. (2017). **Specific alleles of CLN7/MFSD8, a protein that localizes to photoreceptor synaptic terminals, cause a spectrum of nonsyndromic retinal dystrophy.** *Investigative Ophthalmology and Visual Science*, 58(7), 2906-2914. doi:10.1167/iovs.16-20608

PURPOSE. Recessive mutations in CLN7/MFSD8 usually cause variant late-infantile onset neuronal ceroid lipofuscinosis (vLINCL), a poorly understood neurodegenerative condition, though mutations may also cause nonsyndromic maculopathy. A series of 12 patients with nonsyndromic retinopathy due to novel CLN7/MFSD8 mutation combinations were investigated in this study. METHODS. Affected patients and their family members were recruited in ophthalmic clinics at each center where they were examined by retinal imaging and detailed electrophysiology. Whole exome or genome next generation sequencing was

performed on genomic DNA from at least one affected family member. Immunofluorescence confocal microscopy of murine retina cross-sections were used to localize the protein. RESULTS. Compound heterozygous alleles were identified in six cases, one of which was always p.Glu336Gln. Such combinations resulted in isolated macular disease. Six further cases were homozygous for the variant p.Met454Thr, identified as a founder mutation of South Asian origin. Those patients had widespread generalized retinal disease, characterized by electroretinography as a rod-cone dystrophy with severe macular involvement. In addition, the photopic single flash electroretinograms demonstrated a reduced b- to a-wave amplitude ratio, suggesting dysfunction occurring after phototransduction. Immunohistology identified MFSD8 in the outer plexiform layer of the retina, a site rich in photoreceptor synapses. CONCLUSIONS. This study highlights a hierarchy of MFSD8 variant severity, predicting three consequences of mutation: (1) nonsyndromic localized maculopathy, (2) nonsyndromic widespread retinopathy, or (3) syndromic neurological disease. The data also shed light on the underlying pathogenesis by implicating the photoreceptor synaptic terminals as the major site of retinal disease. © 2017 The Authors.

Khanna, V., Eide, C. A., Tognon, C. E., Maxson, J. E., Wilmot, B., Bottomly, D., . . . Tyner, J. W. (2017). **Recurrent cyclin D2 mutations in myeloid neoplasms.** *Leukemia*. doi:10.1038/leu.2017.195

Leukemia accepted article preview online, 20 June 2017. doi:10.1038/leu.2017.195.

Khuu, L. A., Tayyari, F., Sivak, J. M., Flanagan, J. G., Singer, S., Brent, M. H., . . . Hudson, C. (2017). **Aqueous humor endothelin-1 and total retinal blood flow in patients with non-proliferative diabetic retinopathy.** *Eye (London, England)*. doi:10.1038/eye.2017.74

PurposeThe purpose of this study was to determine the association between aqueous ET-1 levels and total retinal blood flow (TRBF) in patients with non-insulin-dependent type 2 diabetes mellitus (T2DM) and early non-proliferative diabetic retinopathy (NPDR). **Patients and methods**A total of 15 age-matched controls and 15 T2DM patients with NPDR were recruited into the study. Aqueous humor (~80-120 µl) was collected before cataract surgery to measure the levels of ET-1 using suspension multiplex array technology. Four weeks post surgery, six images were acquired to assess TRBF using the prototype RTVue Doppler FD-OCT (Optovue, Inc., Fremont, CA, USA) with a double circular scan protocol. At the same visit, forearm blood was collected to determine plasma glycosylated hemoglobin (A1c) levels. **Results**Aqueous ET-1 was significantly elevated in the NPDR group compared with the control group (3.5±1.8 vs 2.2±0.8, P=0.02). TRBF was found to be significantly reduced in the NPDR group compared with the control group (34.5±9.1 vs 44.1±4.6 µl/min, P=0.002). TRBF and aqueous ET-1 were not correlated within the NPDR group (r=-0.24, P=0.22). In a multivariate analysis, high A1c was associated with reduced TRBF and aqueous ET-1 levels across control and NPDR groups (P<0.01). **Conclusion**Aqueous ET-1 levels were increased while TRBF was reduced in patients with NPDR compared with the control group. Although not directly associated, the vasoconstrictory effects of ET-1 are consistent with a reduced TRBF observed in early DR. ET-1 dysregulation may contribute to a reduction in retinal blood flow during early DR. *Eye* advance online publication, 26 May 2017; doi:10.1038/eye.2017.74.

King, W. C., Chen, J. Y., Belle, S. H., Courcoulas, A. P., Dakin, G. F., Flum, D. R., . . . Steffen, K. J. (2017). **Use of prescribed opioids before and after bariatric surgery: Prospective evidence from a U.S. multicenter cohort study.** *Surgery for Obesity and Related Diseases*. doi:10.1016/j.soard.2017.04.003

Background: Limited evidence suggests bariatric surgery may not reduce opioid analgesic use, despite improvements in pain. **Objective:** To determine if use of prescribed opioid analgesics changes in the short and long term after bariatric surgery and to identify factors associated with continued and postsurgery initiated use. **Setting:** Ten U.S. hospitals. **Methods:** The Longitudinal Assessment of Bariatric Surgery-2 is an observational cohort study. Assessments were conducted presurgery, 6 months postsurgery, and annually postsurgery for up to 7 years until January 2015. Opioid use was defined as self-reported daily, weekly, or "as needed" use of

a prescribed medication classified as an opioid analgesic. Results: Of 2258 participants with baseline data, 2218 completed follow-up assessment(s) (78.7% were female, median body mass index: 46; 70.6% underwent Roux-en-Y gastric bypass). Prevalence of opioid use decreased after surgery from 14.7% (95% CI: 13.3-16.2) at baseline to 12.9% (95% CI: 11.5-14.4) at month 6 but then increased to 20.3%, above baseline levels, as time progressed (95% CI: 18.2-22.5) at year 7. Among participants without baseline opioid use (n = 1892), opioid use prevalence increased from 5.8% (95% CI: 4.7-6.9) at month 6 to 14.2% (95% CI: 12.2-16.3) at year 7. Public versus private health insurance, more pain presurgery, undergoing subsequent surgeries, worsening or less improvement in pain, and starting or continuing nonopioid analgesics postsurgery were significantly associated with higher risk of postsurgery initiated opioid use. Conclusion: After bariatric surgery, prevalence of prescribed opioid analgesic use initially decreased but then increased to surpass baseline prevalence, suggesting the need for alternative methods of pain management in this population. © 2017 American Society for Metabolic Bariatric Surgery.

Kirby, M. A., Nagel, C. L., Rosa, G., Umupfasoni, M. M., Iyakaremye, L., Thomas, E. A., & Clasen, T. F. (2017). **Use, microbiological effectiveness and health impact of a household water filter intervention in rural Rwanda-A matched cohort study.** *International Journal of Hygiene and Environmental Health*. doi:10.1016/j.ijheh.2017.05.013

Unsafe drinking water is a substantial health risk contributing to child diarrhoea. We investigated impacts of a program that provided a water filter to households in rural Rwandan villages. We assessed drinking water quality and reported diarrhoea 12-24 months after intervention delivery among 269 households in the poorest tertile with a child under 5 from 9 intervention villages and 9 matched control villages. We also documented filter coverage and use. In Round 1 (12-18 months after delivery), 97.4% of intervention households reported receiving the filter, 84.5% were working, and 86.0% of working filters contained water. Sensors confirmed half of households with working filters filled them at least once every other day on average. Coverage and usage was similar in Round 2 (19-24 months after delivery). The odds of detecting faecal indicator bacteria in drinking water were 78% lower in the intervention arm than the control arm (odds ratio (OR) 0.22, 95% credible interval (CrI) 0.10-0.39, p < .0001). The intervention arm also had 50% lower odds of reported diarrhoea among children <5 than the control arm (OR = 0.50, 95% CrI 0.23-0.90, p = 0.03). The protective effect of the filter is also suggested by reduced odds of reported diarrhoea-related visits to community health workers or clinics, although these did not reach statistical significance. © 2017 Elsevier GmbH.

Kline, C. D., & Blackburn, N. J. (2016). **Substrate-Induced Carbon Monoxide Reactivity Suggests Multiple Enzyme Conformations at the Catalytic Copper M-Center of Peptidylglycine Monooxygenase.** *Biochemistry*, 55(48), 6652-6661. doi:10.1021/acs.biochem.6b00845

The present study uses CO as a surrogate for oxygen to probe how substrate binding triggers oxygen activation in peptidylglycine monooxygenase (PHM). Infrared stretching frequencies ($\nu(\text{C}=\text{O})$) of the carbonyl (CO) adducts of copper proteins are sensitive markers of Cu(I) coordination and are useful in probing oxygen reactivity because the electronic properties of O₂ and CO are similar. The carbonyl chemistry has been explored using PHM WT and a number of active site variants in the absence and presence of peptidyl substrates. We have determined that upon carbonylation (i) a major CO band at 2092 cm⁻¹ and a second minor CO band at 2063 cm⁻¹ are observed in the absence of peptide substrate Ac-YVG; (ii) the presence of peptide substrate amplifies the minor CO band and causes it to partially interconvert with the CO band at 2092 cm⁻¹; (iii) the substrate-induced CO band is associated with a second conformer at CuM; and (iv) the CuH-site mutants, which are inactive, fail to generate any substrate-induced CO bands. The total intensity of both bands is constant, suggesting that the Cu(I)M-site partitions between the two carbonylated enzyme states. Together, these data provide evidence for two conformers at CuM, one of which is induced by binding of the peptide substrate with the implication that this represents the conformation that also allows binding and activation of O₂.

Knupp, K. G., Leister, E., Coryell, J., Nickels, K. C., Ryan, N., Juarez-Colunga, E., . . . Hamikawa, L. (2016). **Response to second treatment after initial failed treatment in a multicenter prospective infantile spasms cohort.** *Epilepsia*, 57(11), 1834-1842. doi:10.1111/epi.13557

OBJECTIVE: Infantile spasms (IS) represent a severe epileptic encephalopathy presenting in the first 2 years of life.

Recommended first-line therapies (hormonal therapy or vigabatrin) often fail. We evaluated response to second treatment for IS in children in whom the initial therapy failed to produce both clinical remission and electrographic resolution of hypsarhythmia and whether time to treatment was related to outcome.

METHODS: The National Infantile Spasms Consortium established a multicenter, prospective database enrolling infants with new diagnosis of IS. Children were considered nonresponders to first treatment if there was no clinical remission or persistence of hypsarhythmia. Treatment was evaluated as hormonal therapy (adrenocorticotrophic hormone [ACTH] or oral corticosteroids), vigabatrin, or "other." Standard treatments (hormonal and vigabatrin) were compared to all other nonstandard treatments. We compared response rates using chi-square tests and multivariable logistic regression models. RESULTS: One hundred eighteen infants were included from 19 centers. Overall response rate to a second treatment was 37% (n = 44). Children who received standard medications with differing mechanisms for first and second treatment had higher response rates than other sequences (27/49 [55%] vs. 17/69 [25%], p < 0.001). Children receiving first treatment within 4 weeks of IS onset had a higher response rate to second treatment than those initially treated later (36/82 [44%] vs. 8/34 [24%], p = 0.040). SIGNIFICANCE: Greater than one third of children with IS will respond to a second medication. Choosing a standard medication (ACTH, oral corticosteroids, or vigabatrin) that has a different mechanism of action appears to be more effective. Rapid initial treatment increases the likelihood of response to the second treatment.

Kopp, R. P., & Tessier, C. D. (2017). **Editorial Commentary.** *Urology Practice*, 4(4), 283-284. doi:10.1016/j.urpr.2016.07.019

Korthuis, P. T., McCarty, D., Weimer, M., Bougatsos, C., Blazina, I., Zakher, B., . . . Chou, R. (2017). **Primary care-based models for the treatment of opioid use disorder: A scoping review.** *Annals of Internal Medicine*, 166(4), 268-278. doi:10.7326/M16-2149

Greater integration of medication-assisted treatment (MAT) for opioid use disorder (OUD) in U.S. primary care settings would expand access to treatment for this condition. Models for integrating MAT into primary care vary in structure. This article summarizes findings of a technical report for the Agency for Healthcare Research and Quality describing MAT models of care for OUD, based on a literature review and interviews with key informants in the field. The report describes 12 representative models of care for integrating MAT into primary care settings that could be considered for adaptation across diverse health care settings. Common components of existing care models include pharmacotherapy with buprenorphine or naltrexone, provider and community education, coordination and integration of OUD treatment with other medical and psychological needs, and psychosocial services and interventions. Models vary in how each component is implemented. Decisions about adopting MAT models of care should be individualized to address the unique milieu of each implementation setting. © 2017 American College of Physicians.

Krey, J. F., Krystofiak, E. S., Dumont, R. A., Vijayakumar, S., Choi, D., Rivero, F., . . . Barr-Gillespie, P. G. (2016). **Plastin 1 widens stereocilia by transforming actin filament packing from hexagonal to liquid.** *J Cell Biol*, 215(4), 467-482. doi:10.1083/jcb.201606036

With their essential role in inner ear function, stereocilia of sensory hair cells demonstrate the importance of cellular actin protrusions. Actin packing in stereocilia is mediated by cross-linkers of the plastin, fascin, and espin families. Although mice lacking espin (ESPN) have no vestibular or auditory function, we found that mice that

either lacked plastin 1 (PLS1) or had nonfunctional fascin 2 (FSCN2) had reduced inner ear function, with double-mutant mice most strongly affected. Targeted mass spectrometry indicated that PLS1 was the most abundant cross-linker in vestibular stereocilia and the second most abundant protein overall; ESPN only accounted for approximately 15% of the total cross-linkers in bundles. Mouse utricle stereocilia lacking PLS1 were shorter and thinner than wild-type stereocilia. Surprisingly, although wild-type stereocilia had random liquid packing of their actin filaments, stereocilia lacking PLS1 had orderly hexagonal packing. Although all three cross-linkers are required for stereocilia structure and function, PLS1 biases actin toward liquid packing, which allows stereocilia to grow to a greater diameter.

Krieg, S. A., Shahine, L. K., & Lathi, R. B. (2016). **Environmental exposure to endocrine-disrupting chemicals and miscarriage.** *Fertility and Sterility*, 106(4), 941-947. doi:10.1016/j.fertnstert.2016.06.043

Establishment of early pregnancy is the result of complex biochemical interactions between the decidua and blastocyst. Any alteration in this chemical dialogue has the potential to result in adverse pregnancy outcomes including miscarriage. Sporadic miscarriage is the most common complication of pregnancy and can be caused by multiple factors. While the most common cause of miscarriage is genetic abnormalities in the fetus, other contributing factors certainly can play a role in early loss. One such factor is environmental exposure, in particular to endocrine-disrupting chemicals, which has the potential to interfere with endogenous hormone action. These effects can be deleterious, especially in early pregnancy when the hormonal milieu surrounding implantation is in delicate balance. The purpose of this paper is to review the current evidence on the role of environmental toxins in reproduction.

Laboissonniere, L. A., Martin, G. M., Goetz, J. J., Bi, R., Pope, B., Weinand, K., . . . Trimarchi, J. M. (2017). **Single cell transcriptome profiling of developing chick retinal cells.** *Journal of Comparative Neurology*, 525(12), 2735-2781. doi:10.1002/cne.24241

The vertebrate retina is a specialized photosensitive tissue comprised of six neuronal and one glial cell types, each of which develops in prescribed proportions at overlapping timepoints from a common progenitor pool. While each of these cells has a specific function contributing to proper vision in the mature animal, their differential representation in the retina as well as the presence of distinctive cellular subtypes makes identifying the transcriptomic signatures that lead to each retinal cell's fate determination and development challenging. We have analyzed transcriptomes from individual cells isolated from the chick retina throughout retinogenesis. While we focused our efforts on the retinal ganglion cells, our transcriptomes of developing chick cells also contained representation from multiple retinal cell types, including photoreceptors and interneurons at different stages of development. Most interesting was the identification of transcriptomes from individual mixed lineage progenitor cells in the chick as these cells offer a window into the cell fate decision-making process. Taken together, these data sets will enable us to uncover the most critical genes acting in the steps of cell fate determination and early differentiation of various retinal cell types. © 2017 Wiley Periodicals, Inc.

Laddu, D. R., Cawthon, P. M., Parimi, N., Hoffman, A. R., Orwoll, E., Miljkovic, I., & Stefanick, M. L. (2017). **Trajectories of the relationships of physical activity with body composition changes in older men: the MrOS study.** *BMC Geriatrics*, 17(1). doi:10.1186/s12877-017-0506-4

Background: Excess adiposity gains and significant lean mass loss may be risk factors for chronic disease in old age. Long-term patterns of change in physical activity (PA) and their influence on body composition decline during aging has not been characterized. We evaluated the interrelationships of PA and body composition at the outset and over longitudinal follow-up to changes in older men. Methods: Self-reported PA by the Physical Activity Scale for the Elderly (PASE), clinic body weight, and whole-body lean mass (LM) and fat mass, by dual-energy x-ray absorptiometry (DXA), were assessed in 5964 community-dwelling men aged ≥ 65 years at baseline (2000-2002) and at two subsequent clinic visits up until March 2009 (an average 4.6

and 6.9 years later). Group-based trajectory modeling (GBTM) identified patterns of change in PA and body composition variables. Relationships of PA and body composition changes were then assessed. Results: GBTM identified three discrete trajectory patterns, all with declining PA, associated primarily with initial PA level high-activity (7.2% of men), moderate-activity (50.0%), and low-activity (42.8%). In separate models, GBTM identified eight discrete total weight change groups, five fat mass change groups, and six LM change groups. Joint trajectory modeling by PA and body composition group illustrated significant declines in total weight and LM, whereas fat mass levels were relatively unchanged among high-activity and low-activity-declining groups, and significantly increased in the moderate-activity-declining group. Conclusion: Although patterns of change in PA and body composition were identified, groups were primarily differentiated by initial PA or body composition rather than by distinct trajectories of change in these variables. © 2017 The Author(s).

Ladermann, A., Abrassart, S., Denard, P. J., Tirefort, J., Nowak, A., & Schwitzgubel, A. J. (2017). **Functional recovery following early mobilization after middle third clavicle osteosynthesis for acute fractures or nonunion: A case-control study.** *Orthopaedics & Traumatology, Surgery & Research*. doi:10.1016/j.otsr.2017.03.021

BACKGROUND: Good outcomes have been reported after surgical treatment for acute or nonunion of displaced midshaft clavicle fractures. However, the postoperative rehabilitation and timeline for a complete functional recovery are poorly documented. The purpose of the current study was to evaluate the efficacy of an immediate motion protocol following plate fixation of a midshaft clavicle fracture and to compare functional recovery between acute and nonunion cases. **METHODS:** Between October 2011 and July 2015, all patients above the age of 18, having either an acute or a nonunion of the midshaft clavicle fracture, were considered as potentially eligible for inclusion in this prospective case-control study. Postoperatively, no immobilization was recommended and patients were to undergo rehabilitation protocol consisting of hourly stretching. **RESULTS:** Forty-two patients were included (31 with acute and 11 with delayed fixation) at a mean follow-up of 33 months (range, 12 to 78 months). Surgical complications consisted of one transient frozen shoulder, one delayed union, and two superficial infections. All patients returned to work, retrieved full shoulder range of motion (ROM), and returned to heavy sports and activities. Function returned faster in the acute group compared to the nonunion group based on the SANE score at 2 weeks (73+/-21 vs. 45+/-26 respectively, P=0.01), SANE score at 6 weeks (89+/-15 vs. 66+/-23 respectively, P=0.01), SANE score at 3 months (96+/-10 vs. 85+/-14 respectively, P=0.03), and based on return of full ROM (17+/-25 vs. 44+/-31 days respectively, P=0.01). A trend was observed for nonunion cases needing more time to return to work and sports activities. **CONCLUSION:** Functional outcome is excellent following the treatment of both acute and non-united clavicle fractures, but recovery occurs earlier following acute treatment. An early mobilization rehab protocol can be safely recommended for both types of conditions and may result in substantial healthcare cost-savings, without increasing complication rate and decreasing patient satisfaction. **LEVEL OF EVIDENCE:** Level III; case-control study; treatment study.

Lam, D. (2017). **Improving the evidence for inferior turbinate surgery in children.** *JAMA Otolaryngology - Head and Neck Surgery*, 143(5), 457-458. doi:10.1001/jamaoto.2016.4326

Laurie, A. L., Chen, Y., Chou, R., & Fu, R. (2016). **Meta-analysis of the Impact of Patient Characteristics on Estimates of Effectiveness and Harms of Recombinant Human Bone Morphogenetic Protein-2 in Lumbar Spinal Fusion.** *Spine (Phila Pa 1976)*, 41(18), E1115-1123. doi:10.1097/brs.0000000000001580

STUDY DESIGN: Meta-analysis of individual patient data from randomized controlled trials of recombinant human bone morphogenetic protein-2 (rhBMP-2) in lumbar spinal fusion. **OBJECTIVE:** To determine how patient characteristics impact estimates of effectiveness and harms of rhBMP-2 versus iliac crest bone graft (ICBG) in lumbar spinal fusion. **SUMMARY OF BACKGROUND DATA:** Patient characteristics are thought to impact rates

of fusion in spinal fusion surgery, but no analyses examining the effect of patient characteristics on efficacy and safety of rhBMP-2 as compared with ICBG have been conducted. METHODS: Using individual patient data obtained from the Yale Open Data Access Project, the impact of patient characteristics on the effects of rhBMP-2 on fusion, overall success, and harms were assessed using linear and generalized linear mixed effects models. RESULTS: Ten industry-sponsored randomized controlled trials of rhBMP-2 were included in the analysis. There is preliminary support for an association between rhBMP-2 and improved outcomes for smokers ($P = 0.01$), individuals under the age of 60 years ($P < 0.01$), and patients of normal weight ($P = 0.03$), but not in patients who are nonsmokers, over the age of 60 years, obese or severely obese. RhBMP-2 usage was associated with decreased harms in individuals with no previous back surgeries but this was not seen in individuals with a previous back surgery ($P < 0.01$). CONCLUSION: Effects of rhBMP-2 may vary according to patient characteristics. Future studies of rhBMP-2 should include planned subgroup analysis in patients over 60 years, smokers, patients that are obese and severely obese, and individuals with previous back surgeries to better identify those most likely to benefit. LEVEL OF EVIDENCE: 1.

Lawler, M., Haussler, D., Siu, L. L., Haendel, M. A., McMurry, J. A., Knoppers, B. M., . . . Sawyers, C. L. (2017). **Sharing Clinical and Genomic Data on Cancer - The Need for Global Solutions.** *N Engl J Med*, 376(21), 2006-2009. doi:10.1056/NEJMp1612254

Lee, C. S., Gelow, J. M., Chien, C. V., Hiatt, S. O., Bidwell, J. T., Denfeld, Q. E., . . . Mudd, J. O. (2017). **Implant Strategy-Specific Changes in Symptoms in Response to Left Ventricular Assist Devices.** *Journal of Cardiovascular Nursing*. doi:10.1097/JCN.0000000000000430

BACKGROUND:: Although we know that the quality of life generally improves after left ventricular assist device (LVAD) implantation, we know little about how symptoms change in response to LVAD. METHODS:: The purpose of this study was to compare the changes in symptoms between bridge and destination therapy patients as part of a prospective cohort study. Physical (dyspnea and wake disturbances) and affective symptoms (depression and anxiety) were measured before LVAD and at 1, 3, and 6 months after LVAD. Multiphase growth modeling was used to capture the 2 major phases of change: initial improvements between preimplant and 1 month after LVAD and subsequent improvements between 1 and 6 months after LVAD. RESULTS:: The sample included 64 bridge and 22 destination therapy patients as the preimplant strategy. Destination patients had worse preimplant dyspnea and wake disturbances, and they experienced greater initial improvements in these symptoms compared with bridge patients (all $P < .05$); subsequent change in both symptoms were similar between groups (both $P > .05$). Destination patients had worse preimplant depression ($P = .042$) but experienced similar initial and subsequent improvements in depression in response to LVAD compared with bridge patients (both $P > .05$). Destination patients had similar preimplant anxiety ($P = .279$) but experienced less initial and greater subsequent improvements in anxiety after LVAD compared with bridge patients (both $P < .05$). CONCLUSION:: There are many differences in the magnitude and timing of change in symptom responses to LVAD between bridge and destination therapy patients. Detailed information on changes in specific symptoms may better inform shared decision-making regarding LVAD. Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved

Lee, M., Sobralske, M., Raney, E., & Carino, B. (2016). **Interpretation time in an ethnically diverse pediatric orthopedic clinic.** *J Health Organ Manag*, 30(4), 530-540. doi:10.1108/jhom-02-2015-0028

Purpose - The purpose of this paper is to determine whether there were differences in clinical encounter time between patients who speak English and those who require an interpretation service in an ethnically diverse pediatric clinic. Design/methodology/approach - Encounter time with patients requiring interpretation was compared to encounter time with patients who spoke English. The sample consisted of 310 encounters at a pediatric orthopedic clinic where patients spoke over 18 primary languages. Data were analyzed using ANOVA to compare four types of encounters. Findings - Approximately 12 percent ($n=38$) required

interpretation and encounters requiring interpretation took 30 percent (nine minutes) longer than those that did not, $p < 0.01$ (25 vs 16 minutes). Furthermore, this difference was mainly among new patients: Approximately, 53 percent increase in time for new patient encounters requiring interpretation (36 vs 23 minutes) while only 25 percent increase in encounter time for established patients (20 vs 16 minutes) was detected. Research limitations/implications - Preventing problems due to language barriers requires time for interpretation which places demands on staff resources and presents clinical challenges. However, long-term benefits of quality health care outweigh the costs associated with interpretation service. Originality/value - To the knowledge, this is the first study to investigate actual encounter time differences in a pediatric clinical setting. The authors found that clinical encounters requiring interpretation took approximately nine minutes longer in general and four minutes longer for established patients. These findings could give much needed information for hospital administrators to allocate appropriate amounts of time and resources to care for those who need interpretation services. However, they also indicate a broader concern of the reduction of clinical encounter time for overall health care system in the country that might need further investigation.

Lei, B. Z., Shatzel, J. J., & Sendowski, M. (2017). **Rapid and durable response to intravenous immunoglobulin in delayed heparin-induced thrombocytopenia: a case report.** *Transfusion*, 57(4), 919-923. doi:10.1111/trf.13960

BACKGROUND: Heparin-induced thrombocytopenia (HIT) results in platelet consumption and a virulent thrombotic state, which generally responds to cessation of heparin and initiation of anticoagulation. Rarely, delayed HIT can occur and/or persist after heparin is discontinued. **STUDY DESIGN AND METHODS:** A 47-year-old male developed delayed HIT with severe thrombocytopenia and thrombosis after cardiac surgery. Thrombocytopenia developed and persisted after heparin cessation and did not improve despite sequential use of argatroban followed by bivalirudin. Treatment with intravenous immunoglobulin (IVIg) was well tolerated and resulted in rapid resolution of thrombocytopenia. **RESULTS:** There are few case reports on the management of delayed HIT with severe and prolonged thrombocytopenia. The risk for thrombosis and bleeding in the setting of an undefined time course increases uncertainty in management. **CONCLUSION:** This case, along with others accumulating in the literature, suggest that IVIg may be effective in treating delayed HIT with persistent thrombocytopenia.

Levy, J. M., Mace, J. C., Bodner, T. E., Alt, J. A., & Smith, T. L. (2017). **Defining the minimal clinically important difference for olfactory outcomes in the surgical treatment of chronic rhinosinusitis.** *Int Forum Allergy Rhinol.* doi:10.1002/alr.21964

BACKGROUND: Olfactory dysfunction is a common and defining symptom of chronic rhinosinusitis (CRS). Many measures of olfactory dysfunction in CRS are limited by scoring criteria defined within general populations with interpretations of statistical significance to infer clinically meaningful improvement. In this investigation we define a minimal clinically important difference (MCID) for the Brief Smell Identification Test (BSIT) in CRS patients electing endoscopic sinus surgery (ESS). **METHODS:** A multicenter cohort of 290 adult patients electing ESS for medically recalcitrant CRS were prospectively enrolled between March 2011 and June 2015 and completed BSIT evaluations before and after ESS. Distribution and anchor-based analytic approaches were utilized to define MCID values of the BSIT across patient cofactors. **RESULTS:** A total of 92 (reverse similar 32%) patients were found to have preoperative olfactory dysfunction (BSIT <9), significantly associated with nasal polyposis ($\chi^2 = 35.0$; $p < 0.001$). The effect-size distribution-based approach identified 1.0 as a MCID criterion value between "small" and "medium" effect (range, 0.61-1.52) overall. Significant mean postoperative change (DeltaM) was reported for patients with olfactory dysfunction (DeltaM = 2.28; $p < 0.001$), both with ($n = 54$; DeltaM = 2.52; $p < 0.001$) and without ($n = 38$; DeltaM = 1.95; $p < 0.001$) nasal polyposis, significantly exceeding the MCID criterion. Anchor-based approaches with regression modeling confirmed associations between MCID values and postoperative changes to olfactory-specific survey responses ($p < 0.001$). **CONCLUSION:** Clinically meaningful change in BSIT scores may be defined as an absolute value difference of at least 1.0 unit for heterogeneous patients electing ESS for CRS. Significantly

exceeding this criterion may be restricted to CRS patients with baseline olfactory dysfunction, regardless of nasal polyposis.

Lim, L. L., Xie, J., Chua, C. C., Wong, T., Hoang, L. T., Becker, M. D., . . . Mackensen, F. (2017). **In Vivo Laser Confocal Microscopy Using the HRT-Rostock Cornea Module: Diversity and Diagnostic Implications in Patients with Uveitis.** *Ocul Immunol Inflamm*, 1-10. doi:10.1080/09273948.2017.1298818

PURPOSE: Keratic precipitates (KP) are a common feature of uveitis. We prospectively examined KP with the Heidelberg Retinal Tomograph II confocal laser scanning microscope and Rostock Corneal Module (HRT-RCM) to explore their diagnostic implications. METHODS: Prospective, observational, multicenter study. HRT-RCM images were classified by two masked observers. RESULTS: 120 scans on 120 eyes from 110 subjects were included. The majority (N = 93) had non-infectious uveitis. Sixty eyes had active disease at scanning. Eight KP morphologies were defined. Agreement between the two masked graders was high (Kappa value across all categories = 0.81). Cluster and nodular KP were associated with active infectious uveitis (p < 0.01): patients with cluster KP (odds ratio [OR] = 3.03, 95% confidence interval [CI]: 1.43, 6.45) and nodular KP (OR = 3.89, 95% CI: 1.42, 10.65) were more likely to have infectious uveitis than those without. CONCLUSIONS: Laser confocal microscopy of KP may have a role in determining between infectious and non-infectious uveitis.

Liu, C., Guo, C., Wang, W., Zhu, P., Li, W., Mi, Y., . . . Sun, K. (2016). **Inhibition of Lysyl Oxidase by Cortisol Regeneration in Human Amnion: Implications for Rupture of Fetal Membranes.** *Endocrinology*, 157(10), 4055-4065. doi:10.1210/en.2016-1406

The mechanisms underlying human parturition are still not understood, yet we need this knowledge to combat preterm birth. Fetal membranes express abundant 11beta-hydroxysteroid dehydrogenase 1 (11beta-HSD1), which converts inert cortisone to active cortisol. We examined whether cortisol regeneration in the amnion might play a role in human parturition through regulation of lysyl oxidase (LOX), a collagen cross-linking enzyme, thereby contributing to the rupture of fetal membranes. By using cultured human primary amnion fibroblasts, we demonstrated that, in addition to the induction of the key enzymes involved in prostaglandin E2 (PGE2) synthesis, cortisol stimulated 11beta-HSD1 and inhibited LOX reciprocally. These results were reproduced in human amnion tissue explants after cortisol treatment. Cortisone also inhibited LOX expression, which was abolished by the inhibition of 11beta-HSD1. Despite the inhibition of LOX by PGE2, inhibition of the PGE2 pathway failed to block the inhibition of LOX by cortisol. However, inhibition of glucocorticoid receptor and mutation of a negative glucocorticoid response element in LOX promoter abolished the inhibition of LOX by cortisol. Chromatin immunoprecipitation assay revealed that cortisol increased GR binding to the LOX promoter. Moreover, increased cortisol and 11beta-HSD1 abundance and decreased LOX abundance were observed in human amnion tissue after the labor-initiated spontaneous rupture of membranes. These data highlight a crucial role for local cortisol regeneration by 11beta-HSD1 in the down-regulation of LOX expression via glucocorticoid receptor binding to a negative glucocorticoid response element to its promoter in the amnion, which may contribute to rupture of fetal membranes at parturition.

Lomis, K., Amiel, J. M., Ryan, M. S., Esposito, K., Green, M., Stagnaro-Green, A., . . . Mejicano, G. C. (2017). **Implementing an Entrustable Professional Activities Framework in Undergraduate Medical Education: Early Lessons From the AAMC Core Entrustable Professional Activities for Entering Residency Pilot.** *Acad Med*, 92(6), 765-770. doi:10.1097/acm.0000000000001543

In 2014, the Association of American Medical Colleges (AAMC) published a list of 13 Core Entrustable Professional Activities for Entering Residency (Core EPAs) that medical school graduates might be expected to perform, without direct supervision, on the first day of residency. Soon after, the AAMC commissioned a five-year pilot with 10 medical schools across the United States, seeking to implement the Core EPA framework to improve

the transition from undergraduate to graduate medical education. In this article, the pilot team presents the organizational structure and early results of collaborative efforts to provide guidance to other institutions planning to implement the Core EPA framework. They describe the aims, timeline, and organization of the pilot as well as findings to date regarding the concepts of entrustment, assessment, curriculum development, and faculty development. On the basis of their experiences over the first two years of the pilot, the authors offer a set of guiding principles for institutions intending to implement the Core EPA framework. They also discuss the impact of the pilot, its limitations, and next steps, as well as how the pilot team is engaging the broader medical education community. They encourage ongoing communication across institutions to capitalize on the expertise of educators to tackle challenges related to the implementation of this novel approach and to generate common national standards for entrustment. The Core EPA pilot aims to better prepare medical school graduates for their professional duties at the beginning of residency with the ultimate goal of improving patient care.

Louis Sam Titus, A. S. C., Yusuff, T., Cassar, M., Thomas, E., Kretschmar, D., & D'Mello, S. R. (2017). **Reduced expression of Foxp1 as a contributing factor in Huntington's disease.** *J Neurosci.* doi:10.1523/jneurosci.3612-16.2017

Huntington's disease (HD) is an inherited neurodegenerative disease caused by a polyglutamine expansion in the huntington protein (htt). The neuropathological hallmark of HD is the loss of neurons in the striatum and, to a lesser extent, in the cortex. Foxp1 is a member of the Forkhead family of transcription factors expressed selectively in the striatum and the cortex. In the brain, three major Foxp1 isoforms are expressed - isoform-A (approximately 90 kDa), isoform-D (approximately 70 kDa) and isoform-C (approximately 50 kDa). We find that expression of Foxp1 isoforms A and D is selectively reduced in the striatum and cortex of R6/2 HD mice as well as in the striatum of HD patients. Furthermore, expression of mutant htt in neurons results in the downregulation of Foxp1. Elevating expression of isoform A or D protects cortical neurons from death caused by the expression of mutant htt. On the other hand, knockdown of Foxp1 promotes death in otherwise healthy neurons. Neuroprotection by Foxp1 is likely to be mediated by the transcriptional stimulation of the cell cycle inhibitory protein, p21Waf1/Cip1. Consistently, Foxp1 activates transcription of the p21Waf1/Cip1 gene promoter and overexpression of Foxp1 in neurons results in the elevation of p21 expression. Moreover, knocking down of p21Waf1/Cip1 blocks the ability of Foxp1 to protect neurons from mutant Htt-induced neurotoxicity. We propose that the selective vulnerability of neurons of the striatum and cortex in HD is related to the loss of expression of Foxp1, a protein that is highly expressed in these neurons and required for their survival. **SIGNIFICANCE STATEMENT** Although the mutant huntingtin gene is expressed widely, neurons of the striatum and cortex are selectively affected in Huntington's disease (HD). Our results suggest that this selectivity is due to the reduced expression of Foxp1, a protein expressed selectively in striatal and cortical neurons which plays a neuroprotective role in these cells. We show that protection by Foxp1 involves stimulation of the p21Waf1/Cip1 (Cdkn1a) gene. Although three major Foxp1 isoforms (A, C and D) are expressed in the brain, only isoform-A has been studied in the nervous system. We show that isoform-D is also expressed selectively, neuroprotective and downregulated in HD mice and patients. Our results suggest that Foxp1 might be an attractive therapeutic target for HD.

Lusk, J., Dobscha, S. K., Kopacz, M., Frances Ritchie, M., & Ono, S. (2017). **Spirituality, Religion and Suicidality Among Veterans: A Qualitative Study.** *Arch Suicide Res.* doi:10.1080/13811118.2017.1340856

OBJECTIVES: This qualitative study explores the relationship between Veterans' spirituality/religion and suicide ideation and attempts. **METHODS:** Qualitative semi-structured interviews were conducted with 30 Veterans who either endorsed chronic suicidal ideation or had made suicide attempt(s). Interviews explored the bi-directional relationship between spirituality/religion (e.g., beliefs, practices and experiences), and suicide ideation and behaviors. Interviews were analyzed using thematic analysis. **RESULTS:** Veterans' responses indicate that spirituality/religion can discourage or permit suicidal ideation, help in coping with ideation, and facilitate meaning making and coping in the presence of self-perceived suffering. Veterans who survived a suicide attempt explored the impact of their spirituality/religion on their recovery. **CONCLUSION:** Findings

highlight a complex and diverse relationship between spirituality/religion and suicidality. These findings may inform further research on treatment strategies that assess the function of spirituality/religion, and incorporate protective aspects of spirituality/religion into mental health treatment.

Luxenberg, A., Chan, B., Khanna, R., & Sarkar, U. (2017). **Efficiency and Interpretability of Text Paging Communication for Medical Inpatients: A Mixed-Methods Analysis.** *JAMA Intern Med.* doi:10.1001/jamainternmed.2017.2133

Madden, C. J., & Morrison, S. F. (2016). **A high-fat diet impairs cooling-evoked brown adipose tissue activation via a vagal afferent mechanism.** *American Journal of Physiology: Endocrinology and Metabolism*, 311(2), E287-292. doi:10.1152/ajpendo.00081.2016

In dramatic contrast to rats on a control diet, rats maintained on a high-fat diet (HFD) failed to activate brown adipose tissue (BAT) during cooling despite robust increases in their BAT activity following direct activation of their BAT sympathetic premotor neurons in the raphe pallidus. Cervical vagotomy or blockade of glutamate receptors in the nucleus of the tractus solitarius (NTS) reversed the HFD-induced inhibition of cold-evoked BAT activity. Thus, a HFD does not prevent rats from mounting a robust, centrally driven BAT thermogenesis; however, a HFD does alter a vagal afferent input to NTS neurons, thereby preventing the normal activation of BAT thermogenesis to cooling. These results, paralleling the absence of cooling-evoked glucose uptake in the BAT of obese humans, reveal a neural mechanism through which consumption of a HFD contributes to reduced energy expenditure and thus to weight gain.

Marehbian, J., Muehlschlegel, S., Edlow, B. L., Hinson, H. E., & Hwang, D. Y. (2017). **Medical Management of the Severe Traumatic Brain Injury Patient.** *Neurocritical Care*, 1-17. doi:10.1007/s12028-017-0408-5

Severe traumatic brain injury (sTBI) is a major contributor to long-term disability and a leading cause of death worldwide. Medical management of the sTBI patient, beginning with prehospital triage, is aimed at preventing secondary brain injury. This review discusses prehospital and emergency department management of sTBI, as well as aspects of TBI management in the intensive care unit where advances have been made in the past decade. Areas of emphasis include intracranial pressure management, neuromonitoring, management of paroxysmal sympathetic hyperactivity, neuroprotective strategies, prognostication, and communication with families about goals of care. Where appropriate, differences between the third and fourth editions of the Brain Trauma Foundation guidelines for the management of severe traumatic brain injury are highlighted. © 2017 Springer Science+Business Media New York

May, T. L., Gifford, A. H., Lahiri, T., Black, A., Trang, J., Cornell, A. G., . . . Zuckerman, J. B. (2017). **Complications of long and intermediate term venous catheters in cystic fibrosis patients: A multicenter study.** *Journal of Cystic Fibrosis.* doi:10.1016/j.jcf.2017.04.014

Background: Totally implantable venous access devices (TIVADs) or peripherally inserted central venous catheters (PICCs) are commonly used in the care of patients with cystic fibrosis (CF), but they are associated with various complications, including thrombosis, infection, and insertion site symptoms. Methods: We conducted a retrospective review of PICC and TIVAD use in adults and children with CF over an 8-year period at 3 accredited care centers. Patient attributes included CFTR genotype, comorbidities, lung function, body mass index, use of anticoagulation, and respiratory tract microbiology. Catheter data included line type, caliber, and lumen number. We assessed practice variation by surveying physicians. Results: In a population of 592 CF patients, 851 PICC and 61 TIVADs were placed between January 1, 2003 and July 1, 2011. Larger catheter caliber and increased lumen number were risk factors for PICC complications in adults. Patient-related risk factors for PICC complications included poor nutritional status, infection with *Burkholderia cepacia* spp., and

having ≥ 5 lines inserted during the study period. The probability of a PICC complication varied across centers (2.6% to 14.1%, $p = 0.001$) and remained significant after adjustment for patient- and line-related risk factors. The median complication-free survival of TIVADs, however, did not vary significantly by center ($p = 0.85$). Conclusions: This is the first longitudinal, multicenter assessment of complication rates for PICCs and TIVADs in a large cohort of adults and children with CF. Specific patient- and catheter-related characteristics were associated with increased risk of complications. Center effects on complication rates were observed for PICCs. © 2017 European Cystic Fibrosis Society.

McClelland, S., Baker, J. F., Smith, J. S., Line, B. G., Hart, R. A., Ames, C. P., & Bess, R. S. (2016). **Complications and operative spine fusion construct length in Parkinson's disease: A nationwide population-based analysis.** *Journal of Clinical Neuroscience*. doi:10.1016/j.jocn.2017.05.006

There remains a dearth of information regarding the surgical complications following multilevel spine surgery in Parkinson's disease (PD) patients. This retrospective cohort study was performed to address this issue on a nationwide level using the Nationwide Inpatient Sample from 2001 to 2012. More than 25 postoperative variables were analyzed to assess the impact of fusion construct length on each variable. Subsequently, the same analysis was performed on admissions without PD. 4301 PD patients with spine fusion were identified, of whom 934 (21.7%) underwent fusion of at least three levels; the remaining 3367 underwent fusion of 1-2 levels. Patients with 3+ level fusions were more likely to suffer paraplegia ($P = .001$; OR = 3.0; 95%CI = 1.5-6.1), hematoma/seroma ($P = .009$; OR = 1.9; 95%CI = 1.2-3.2), IVC filter placement ($P = .018$; OR = 2.1; 95%CI = 1.1-3.9), RBC transfusion ($P < .001$; OR = 3.2; 95%CI = 2.7-3.8), PE ($P = .027$; OR = 4.5; 95%CI = 1.2-16.9), postoperative shock ($P = .023$; OR = 7.3; 95%CI = 1.3-39.6), ARDS ($P < .001$; OR = 4.1; 95%CI = 2.7-6.3), VTE ($P = .006$; OR = 2.6; 95%CI = 1.3-5.4), acute posthemorrhagic anemia ($P < .001$; OR = 2.0; 95%CI = 1.7-2.4), device-related complications ($P < .001$; OR = 3.1; 95%CI = 2.3-4.2), and in-hospital mortality ($P = .005$; OR = 3.4; 95%CI = 1.5-7.4). 3+ level fusions were also more likely to have LOS. > 1 week ($P < .001$; OR = 2.1; 95%CI = 1.8-2.5), and a nonroutine discharge ($P = .005$; OR = 1.9; 95%CI = 1.4-2.4). 692,173 non-PD patients with spine fusion were identified; 123,964 (17.9%) underwent 3+ level fusion. Differences between 3+ versus 1-2 level fusions were similar to those in PD patient, but unlike PD patients, postoperative infection was significant while in-hospital mortality, PE and VTE were not. Fusion of at least three levels increased morbidity, mortality, and adverse discharge disposition compared with 1-2 level fusions. Nearly 80% of all spine fusions performed in the United States are fewer than three levels. These findings are worth considering during operative decision-making in both PD and non-PD patients. © 2017 Elsevier Ltd.

McConnell, H. L., Kersch, C. N., Woltjer, R. L., & Neuwelt, E. A. (2017). **The Translational Significance of the Neurovascular Unit.** *J Biol Chem*, 292(3), 762-770. doi:10.1074/jbc.R116.760215

The mammalian brain is supplied with blood by specialized vasculature that is structurally and functionally distinct from that of the periphery. A defining feature of this vasculature is a physical blood-brain barrier (BBB). The BBB separates blood components from the brain microenvironment, regulating the entry and exit of ions, nutrients, macromolecules, and energy metabolites. Over the last two decades, physiological studies of cerebral blood flow dynamics have demonstrated that substantial intercellular communication occurs between cells of the vasculature and the neurons and glia that abut the vasculature. These findings suggest that the BBB does not function independently, but as a module within the greater context of a multicellular neurovascular unit (NVU) that includes neurons, astrocytes, pericytes, and microglia as well as the blood vessels themselves. Here, we describe the roles of these NVU components as well as how they act in concert to modify cerebrovascular function and permeability in health and in select diseases.

McGill, J. B., & Ahmann, A. (2017). **Continuous glucose monitoring with multiple daily insulin treatment: Outcome studies.** *Diabetes Technology and Therapeutics*, 19, S3-S12. doi:10.1089/dia.2017.0090

Continuous glucose monitoring (CGM) is developing into an increasingly useful tool for glucose monitoring and therapeutic guidance in the treatment of diabetes. Multiple daily doses of insulin (MDI) is the most common method for intensive insulin treatment of type 1 diabetes and is also becoming more common in the treatment of type 2 diabetes as an increasing population with type 2 diabetes experiences progressive beta cell loss. The clinical evidence demonstrating the benefit of CGM in the outcomes of patients treated with MDI is becoming clearer, particularly with the recent completion of several randomized clinical trials addressing both type 1 and 2 diabetes. This evidence is reviewed. © Copyright 2017, Mary Ann Liebert, Inc.

McGill, T. J., Bohana-Kashtan, O., Stoddard, J. W., Andrews, M. D., Pandit, N., Rosenberg-Belmaker, L. R., . . . Irving, C. (2017). **Long-Term Efficacy of GMP Grade Xeno-Free hESC-Derived RPE Cells Following Transplantation.** *Transl Vis Sci Technol*, 6(3), 17. doi:10.1167/tvst.6.3.17

PURPOSE: Retinal pigment epithelium (RPE) dysfunction underlies the retinal degenerative process in age-related macular degeneration (AMD), and thus RPE cell replacement provides an optimal treatment target. We characterized longitudinally the efficacy of RPE cells derived under xeno-free conditions from clinical and xeno-free grade human embryonic stem cells (OpRegen) following transplantation into the subretinal space of Royal College of Surgeons (RCS) rats. **METHODS:** Postnatal (P) day 20 to 25 RCS rats (n = 242) received a single subretinal injection of 25,000 (low)-, 100,000 (mid)-, or 200,000 (high)-dose xeno-free RPE cells. BSS+ (balanced salt solution) (vehicle) and unoperated eyes served as controls. Optomotor tracking (OKT) behavior was used to quantify functional efficacy. Histology and immunohistochemistry were used to evaluate photoreceptor rescue and transplanted cell survival at 60, 100, 150, and 200 days of age. **RESULTS:** OKT was rescued in a dose-dependent manner. Outer nuclear layer (ONL) was significantly thicker in cell-treated eyes than controls up to P150. Transplanted RPE cells were identified in both the subretinal space and integrated into the host RPE monolayer in animals of all age groups, and often contained internalized photoreceptor outer segments. No pathology was observed. **CONCLUSIONS:** OpRegen RPE cells survived, rescued visual function, preserved rod and cone photoreceptors long-term in the RCS rat. Thus, these data support the use of OpRegen RPE cells for the treatment of human RPE cell disorders including AMD. **TRANSLATIONAL RELEVANCE:** Our novel xeno-free RPE cells minimize concerns of animal derived contaminants while providing a promising prospective therapy to the diseased retina.

McGinley, K. F., Sun, X., Howard, L. E., Aronson, W. J., Terris, M. K., Kane, C. J., . . . Freedland, S. J. (2017). **Characterization of a "low-risk" cohort of grade group 2 prostate cancer patients: Results from the Shared Equal Access Regional Cancer Hospital database.** *International Journal of Urology*. doi:10.1111/iju.13387

Objectives: To examine if there is a subset of men with grade group 2 prostate cancer who could be potential candidates for active surveillance. **Methods:** We used the Shared Equal Access Regional Cancer Hospital database to identify 776 men undergoing radical prostatectomy from 2006 to 2015 with >8 biopsy cores obtained and complete information. We compared men who fulfilled low-risk disease criteria (clinical stage T1c/T2a; grade group 1; prostate-specific antigen ≤ 10 ng/mL) with the exception of grade group 2 versus men who met all three low-risk criteria. Logistic regression was used to test the association between grade group and radical prostatectomy pathological features. Biochemical recurrence was examined using Cox models. To examine whether there was a subset of men with low-volume grade group 2 with comparable outcomes to low-risk men, we repeated all analyses limiting the percentage of positive cores in the grade group 2 group to $\leq 33\%$, and positive cores to ≤ 4 , ≤ 3 or ≤ 2 . **Results:** Grade group 2 low-risk men had increased risk of pathological grade group 3 or higher (P < 0.001), extraprostatic extension (P < 0.001), seminal vesicle invasion (P < 0.001) and higher risk of biochemical recurrence (hazard ratio = 1.76, P = 0.006). Using increasingly strict definitions of low-volume disease, at ≤ 2 positive cores there was no difference in adverse pathology between groups (all P > 0.2), except higher pathological grade group (P = 0.006). Biochemical recurrence was similar in men in grade group 1 and grade group 2 (hazard ratio = 1.24; P = 0.529). **Conclusions:** Among men with prostate-specific antigen ≤ 10 ng/mL and clinical stage T1c/T2a,

those in grade group 2 with ≤ 2 total positive cores have similar rates of adverse pathology and biochemical recurrence as men with grade group 1. © 2017 The Japanese Urological Association.

Messaoudi, I., Handu, M., Rais, M., Sureshchandra, S., Park, B. S., Fei, S. S., . . . Varlamov, O. (2017). **Long-lasting effect of obesity on skeletal muscle transcriptome.** *BMC Genomics*, *18*(1), 411. doi:10.1186/s12864-017-3799-y

BACKGROUND: Reduced physical activity and increased intake of calorically-dense diets are the main risk factors for obesity, glucose intolerance, and type 2 diabetes. Chronic overnutrition and hyperglycemia can alter gene expression, contributing to long-term obesity complications. While caloric restriction can reduce obesity and glucose intolerance, it is currently unknown whether it can effectively reprogram transcriptome to a pre-obesity level. The present study addressed this question by the preliminary examination of the transcriptional dynamics in skeletal muscle after exposure to overnutrition and following caloric restriction. **RESULTS:** Six male rhesus macaques of 12-13 years of age consumed a high-fat western-style diet for 6 months and then were calorically restricted for 4 months without exercise. Skeletal muscle biopsies were subjected to longitudinal gene expression analysis using next-generation whole-genome RNA sequencing. In spite of significant weight loss and normalized insulin sensitivity, the majority of WSD-induced ($n = 457$) and WSD-suppressed ($n = 47$) genes remained significantly dysregulated after caloric restriction ($FDR < / = 0.05$). The MetacoreTM pathway analysis reveals that western-style diet induced the sustained activation of the transforming growth factor-beta gene network, associated with extracellular matrix remodeling, and the downregulation of genes involved in muscle structure development and nutritional processes. **CONCLUSIONS:** Western-style diet, in the absence of exercise, induced skeletal muscle transcriptional programming, which persisted even after insulin resistance and glucose intolerance were completely reversed with caloric restriction.

Meyer, T. J., Rosenkrantz, J. L., Carbone, L., & Chavez, S. L. (2017). **Endogenous retroviruses: With us and against us.** *Frontiers in Chemistry*, *5*(APR). doi:10.3389/fchem.2017.00023

Mammalian genomes are scattered with thousands of copies of endogenous retroviruses (ERVs), mobile genetic elements that are relics of ancient retroviral infections. After inserting copies into the germ line of a host, most ERVs accumulate mutations that prevent the normal assembly of infectious viral particles, becoming trapped in host genomes and unable to leave to infect other cells. While most copies of ERVs are inactive, some are transcribed and encode the proteins needed to generate new insertions at novel loci. In some cases, old copies are removed via recombination and other mechanisms. This creates a shifting landscape of ERV copies within host genomes. New insertions can disrupt normal expression of nearby genes via directly inserting into key regulatory elements or by containing regulatory motifs within their sequences. Further, the transcriptional silencing of ERVs via epigenetic modification may result in changes to the epigenetic regulation of adjacent genes. In these ways, ERVs can be potent sources of regulatory disruption as well as genetic innovation. Here, we provide a brief review of the association between ERVs and gene expression, especially as observed in pre-implantation development and placentation. Moreover, we will describe how disruption of the regulated mechanisms of ERVs may impact somatic tissues, mostly in the context of human disease, including cancer, neurodegenerative disorders, and schizophrenia. Lastly, we discuss the recent discovery that some ERVs may have been pressed into the service of their host genomes to aid in the innate immune response to exogenous viral infections. © 2017 Meyer, Rosenkrantz, Carbone and Chavez.

Miglioretti, D. L., Ichikawa, L., Smith, R. A., Buist, D. S. M., Carney, P. A., Geller, B., . . . Kerlikowske, K. (2017). **Correlation Between Screening Mammography Interpretive Performance on a Test Set and Performance in Clinical Practice.** *Acad Radiol*. doi:10.1016/j.acra.2017.03.016

RATIONALE AND OBJECTIVES: Evidence is inconsistent about whether radiologists' interpretive performance on a screening mammography test set reflects their performance in clinical practice. This study aimed to estimate the correlation between test set and clinical performance and determine if the correlation is influenced by

cancer prevalence or lesion difficulty in the test set. MATERIALS AND METHODS: This institutional review board-approved study randomized 83 radiologists from six Breast Cancer Surveillance Consortium registries to assess one of four test sets of 109 screening mammograms each; 48 radiologists completed a fifth test set of 110 mammograms 2 years later. Test sets differed in number of cancer cases and difficulty of lesion detection. Test set sensitivity and specificity were estimated using woman-level and breast-level recall with cancer status and expert opinion as gold standards. Clinical performance was estimated using women-level recall with cancer status as the gold standard. Spearman rank correlations between test set and clinical performance with 95% confidence intervals (CI) were estimated. RESULTS: For test sets with fewer cancers (N = 15) that were more difficult to detect, correlations were weak to moderate for sensitivity (woman level = 0.46, 95% CI = 0.16, 0.69; breast level = 0.35, 95% CI = 0.03, 0.61) and weak for specificity (0.24, 95% CI = 0.01, 0.45) relative to expert recall. Correlations for test sets with more cancers (N = 30) were close to 0 and not statistically significant. CONCLUSIONS: Correlations between screening performance on a test set and performance in clinical practice are not strong. Test set performance more accurately reflects performance in clinical practice if cancer prevalence is low and lesions are challenging to detect.

Miguel, V., Cui, J. Y., Daimiel, L., Espinosa-Diez, C., Fernandez-Hernando, C., Kavanagh, T. J., & Lamas, S. (2017). **The role of microRNAs in environmental risk factors, noise-induced hearing loss and mental stress.** *Antioxid Redox Signal*. doi:10.1089/ars.2017.7175

SIGNIFICANCE: MicroRNAs (miRNAs) are important regulators of gene expression and define part of the epigenetic signature. Their influence on every realm of biomedicine is established and progressively increasing. The impact of environment on human health is enormous. Among environmental risk factors impinging on quality of life are those of chemical nature (toxic chemicals, heavy metals, pollutants, pesticides) as well as those related to everyday life such as exposure to noise or mental and psychosocial stress. Recent Advances: This review elaborates on the relationship between miRNAs and these environmental risk factors. CRITICAL ISSUES: The most relevant facts underlying the role of miRNAs in the response to these environmental stressors, including redox regulatory changes and oxidative stress are highlighted and discussed. In the cases where miRNA mutations are relevant for this response the pertinent literature is also reviewed. FUTURE DIRECTIONS: We conclude that, even though in some cases important advances have been made regarding close correlations between specific miRNAs and biological responses to environmental risk factors, a need for prospective large-cohort studies is likely necessary to establish causative roles.

Mitchell, T. O., Holihan, J. L., Askenasy, E. P., Greenberg, J. A., Keith, J. N., Martindale, R. G., . . . Liang, M. K. (2016). **Do risk calculators accurately predict surgical site occurrences?** *Journal of Surgical Research*, 203(1), 56-63. doi:10.1016/j.jss.2016.03.040

INTRODUCTION: Current risk assessment models for surgical site occurrence (SSO) and surgical site infection (SSI) after open ventral hernia repair (VHR) have limited external validation. Our aim was to determine (1) whether existing models stratify patients into groups by risk and (2) which model best predicts the rate of SSO and SSI. METHODS: Patients who underwent open VHR and were followed for at least 1 mo were included. Using two data sets—a retrospective multicenter database (Ventral Hernia Outcomes Collaborative) and a single-center prospective database (Prospective)—each patient was assigned a predicted risk with each of the following models: Ventral Hernia Risk Score (VHRS), Ventral Hernia Working Group (VHWG), Centers for Disease Control and Prevention Wound Class, and Hernia Wound Risk Assessment Tool (HW-RAT). Patients in the Prospective database were also assigned a predicted risk from the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP). Areas under the receiver operating characteristic curve (area under the curve [AUC]) were compared to assess the predictive accuracy of the models for SSO and SSI. Pearson's chi-square was used to determine which models were able to risk-stratify patients into groups with significantly differing rates of actual SSO and SSI. RESULTS: The Ventral Hernia Outcomes Collaborative database (n = 795) had an overall SSO and SSI rate of 23% and 17%, respectively. The AUCs were low for SSO (0.56, 0.54, 0.52, and 0.60) and SSI (0.55, 0.53, 0.50, and 0.58). The VHRS (P = 0.01) and HW-RAT (P < 0.01) significantly stratified patients into tiers for SSO, whereas the VHWG (P < 0.05)

and HW-RAT ($P < 0.05$) stratified for SSI. In the Prospective database ($n = 88$), 14% and 8% developed an SSO and SSI, respectively. The AUCs were low for SSO (0.63, 0.54, 0.50, 0.57, and 0.69) and modest for SSI (0.81, 0.64, 0.55, 0.62, and 0.73). The ACS-NSQIP ($P < 0.01$) stratified for SSO, whereas the VHRS ($P < 0.01$) and ACS-NSQIP ($P < 0.05$) stratified for SSI. In both databases, VHRS, VHWG, and Centers for Disease Control and Prevention overestimated risk of SSO and SSI, whereas HW-RAT and ACS-NSQIP underestimated risk for all groups. CONCLUSIONS: All five existing predictive models have limited ability to risk-stratify patients and accurately assess risk of SSO. However, both the VHRS and ACS-NSQIP demonstrate modest success in identifying patients at risk for SSI. Continued model refinement is needed to improve the two highest performing models (VHRS and ACS-NSQIP) along with investigation to determine whether modifications to perioperative management based on risk stratification can improve outcomes.

Morone, K. A., Neimat, J. S., Roe, A. W., & Friedman, R. M. (2017). **Review of functional and clinical relevance of intrinsic signal optical imaging in human brain mapping.** *Neurophotonics*, 4(3), 031220. doi:10.1117/1.NPh.4.3.031220

Intrinsic signal optical imaging (ISOI) within the first decade of its use in humans showed its capacity as a precise functional mapping tool. It is a powerful tool that can be used intraoperatively to help a surgeon to directly identify functional areas of the cerebral cortex. Its use is limited to the intraoperative setting as it requires a craniotomy and durotomy for direct visualization of the brain. It has been applied in humans to study language, somatosensory and visual cortices, cortical hemodynamics, epileptiform activity, and lesion delineation. Despite studies showing clear evidence of its usefulness in clinical care, its clinical use in humans has not grown. Impediments imposed by imaging in a human operating room setting have hindered such work. However, recent studies have been aimed at overcoming obstacles in clinical studies establishing the benefits of its use to patients. This review provides a description of ISOI and its use in human studies with an emphasis on the challenges that have hindered its widespread use and the recent studies that aim to overcome these hurdles. Clinical studies establishing the benefits of its use to patients would serve as the impetus for continued development and use in humans.

Mu, E. W., Lewin, J. M., Stevenson, M. L., Meehan, S. A., Carucci, J. A., & Gareau, D. S. (2016). **Use of Digitally Stained Multimodal Confocal Mosaic Images to Screen for Nonmelanoma Skin Cancer.** *JAMA Dermatol*, 152(12), 1335-1341. doi:10.1001/jamadermatol.2016.2997

Importance: Confocal microscopy has the potential to provide rapid bedside pathologic analysis, but clinical adoption has been limited in part by the need for physician retraining to interpret grayscale images. Digitally stained confocal mosaics (DSCMs) mimic the colors of routine histologic specimens and may increase adaptability of this technology. Objective: To evaluate the accuracy and precision of 3 physicians using DSCMs before and after training to detect basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) in Mohs micrographic surgery fresh-tissue specimens. Design: This retrospective study used 133 DSCMs from 64 Mohs tissue excisions, which included clear margins, residual BCC, or residual SCC. Discarded tissue from Mohs surgical excisions from the dermatologic surgery units at Memorial Sloan Kettering Cancer Center and Oregon Health & Science University were collected for confocal imaging from 2006 to 2011. Final data analysis and interpretation took place between 2014 and 2016. Two Mohs surgeons and a Mohs fellow, who were blinded to the correlating gold standard frozen section diagnoses, independently reviewed the DSCMs for residual nonmelanoma skin cancer (NMSC) before and after a brief training session (about 5 minutes). The 2 assessments were separated by a 6-month washout period. Main Outcomes and Measures: Diagnostic accuracy was characterized by sensitivity and specificity of detecting NMSC using DSCMs vs standard frozen histopathologic specimens. The diagnostic precision was calculated based on interobserver agreement and kappa scores. Paired 2-sample t tests were used for comparative means analyses before and after training. Results: The average respective sensitivities and specificities of detecting NMSC were 90% (95% CI, 89%-91%) and 79% (95% CI, 52%-100%) before training and 99% (95% CI, 99%-99%) ($P = .001$) and 93% (95% CI, 90%-96%) ($P = .18$) after training; for BCC, they were 83% (95% CI, 59%-100%) and 92% (95% CI, 81%-100%) before training and 98% (95% CI, 98%-98%) ($P = .18$) and 97% (95% CI, 95%-100%) ($P = .15$) after training;

for SCC, they were 73% (95% CI, 65%-81%) and 89% (95% CI, 72%-100%) before training and 100% (P = .004) and 98% (95% CI, 95%-100%) (P = .21) after training. The pretraining interobserver agreement was 72% (kappa = 0.58), and the posttraining interobserver agreement was 98% (kappa = 0.97) (P = .04). Conclusions and Relevance: Diagnostic use of DSCMs shows promising correlation to frozen histologic analysis, but image quality was affected by variations in image contrast and mosaic-stitching artifact. With training, physicians were able to read DSCMs with significantly improved accuracy and precision to detect NMSC.

Mukherjee, A., Alzhanov, D., & Rotwein, P. (2016). **Defining human insulin-like growth factor I gene regulation.** *American Journal of Physiology: Endocrinology and Metabolism*, 311(2), E519-529. doi:10.1152/ajpendo.00212.2016

Growth hormone (GH) plays an essential role in controlling somatic growth and in regulating multiple physiological processes in humans and other species. Insulin-like growth factor I (IGF-I), a conserved, secreted 70-amino acid peptide, is a critical mediator of many of the biological effects of GH. Previous studies have demonstrated that GH rapidly and potently promotes IGF-I gene expression in rodents and in some other mammals through the transcription factor STAT5b, leading to accumulation of IGF-I mRNAs and production of IGF-I. Despite this progress, very little is known about how GH or other trophic factors control human IGF1 gene expression, in large part because of the absence of any cellular model systems that robustly express IGF-I. Here, we have addressed mechanisms of regulation of human IGF-I by GH after generating cells in which the IGF1 chromosomal locus has been incorporated into a mouse cell line. Using this model, we found that physiological levels of GH rapidly stimulate human IGF1 gene transcription and identify several potential transcriptional enhancers in chromatin that bind STAT5b in a GH-regulated way. Each of the putative enhancers also activates a human IGF1 gene promoter in reconstitution experiments in the presence of the GH receptor, STAT5b, and GH. Thus we have developed a novel experimental platform that now may be used to determine how human IGF1 gene expression is controlled under different physiological and pathological conditions.

Munks, M. W., Montoya, A. M., Pywell, C. M., Talmage, G., Forssen, A., Campbell, T. L., . . . Marrack, P. (2017). **The domestic cat antibody response to feline herpesvirus-1 increases with age.** *Veterinary Immunology and Immunopathology*, 188, 65-70. doi:10.1016/j.vetimm.2017.05.002

Herpesviruses establish lifelong infections, normally characterized by prolonged periods of latency with intermittent episodes of viral reactivation. Feline herpesvirus-1 (FHV-1) infects domestic cats, and epidemiological studies indicate that many or most domestic cats are exposed to FHV-1, but the strength and longevity of the antibody response to FHV-1 is not fully characterized. Here we describe development of an ELISA, using lysates of cat cells infected with FHV-1, that measure feline antibodies against FHV-1. The assay is sensitive, quantitative and has a large dynamic range. We found that serum anti-FHV-1 antibodies primarily recognize FHV-1 proteins of the Late (L) class and are primarily of the IgG isotype. We then analyzed serum from a cross-sectional cohort of 100 client-owned cats that differed in age, sex and vaccination history. While there was no difference in FHV-1 antibody responses between females and males, antibody levels were significantly increased in older cats in comparison with younger animals (p = 0.01). Surprisingly, as the length of time since the most recent vaccination increased, there was no corresponding drop in serum anti-FHV-1 antibody. These data suggest that FHV-1 immunity is very long-lived and support the current recommendation that many cats do not require revaccination against FHV-1 annually. © 2017 Elsevier B.V.

Murray, S. E., Nesterenko, P. A., Vanarsdall, A. L., Munks, M. W., Smart, S. M., Veziroglu, E. M., . . . Hill, A. B. (2017). **Fibroblast-adapted human CMV vaccines elicit predominantly conventional CD8 T cell responses in humans.** *Journal of Experimental Medicine*. doi:10.1084/jem.20161988

Cytomegalovirus (CMV)-based vaccines have shown remarkable efficacy in the rhesus macaque model of acquired immune deficiency syndrome, enabling 50% of vaccinated monkeys to clear a subsequent virulent simian

immunodeficiency virus challenge. The protective vaccine elicited unconventional CD8 T cell responses that were entirely restricted by MHC II or the nonclassical MHC I molecule, MHC-E. These unconventional responses were only elicited by a fibroblast-adapted rhesus CMV vector with limited tissue tropism; a repaired vector with normal tropism elicited conventional responses. Testing whether these unusual protective CD8 T responses could be elicited in humans requires vaccinating human subjects with a fibroblast-adapted mutant of human CMV (HCMV). In this study, we describe the CD8 T cell responses of human subjects vaccinated with two fibroblast-adapted HCMV vaccines. Most responses were identified as conventional classically MHC I restricted, and we found no evidence for MHC II or HLA-E restriction. These results indicate that fibroblast adaptation alone is unlikely to explain the unconventional responses observed in macaques.

Nakayama, S., Migliati, E., Amiry-Moghaddam, M., Ottersen, O. P., & Bhardwaj, A. (2016). **Osmotherapy With Hypertonic Saline Attenuates Global Cerebral Edema Following Experimental Cardiac Arrest via Perivascular Pool of Aquaporin-4.** *Critical Care Medicine*, 44(8), e702-710. doi:10.1097/ccm.0000000000001671

OBJECTIVES: We tested the hypothesis that osmotherapy with hypertonic saline attenuates cerebral edema following experimental cardiac arrest and cardiopulmonary resuscitation by exerting its effect via the perivascular pool of aquaporin-4. We used mice with targeted disruption of the gene encoding alpha-syntrophin (alpha-Syn) that demonstrate diminished perivascular aquaporin-4 pool but retain the non-endfoot and ependymal pools. **DESIGN:** Laboratory animal study. **SETTING:** University animal research laboratory. **INTERVENTIONS:** Isoflurane-anesthetized adult male wild-type C57B/6 or alpha-Syn mice were subjected to cardiac arrest/cardiopulmonary resuscitation and treated with either a continuous IV infusion of 0.9% saline or various concentrations of hypertonic saline. Serum osmolality, regional brain water content, blood-brain barrier disruption, and aquaporin-4 protein expression were determined at 24 hours after cardiac arrest/cardiopulmonary resuscitation. **MEASUREMENTS AND MAIN RESULTS:** Hypertonic saline (7.5%) treatment significantly attenuated water content in the caudoputamen complex and cortex compared with 0.9% saline treatment in wild-type mice subjected to cardiac arrest/cardiopulmonary resuscitation. In contrast, in alpha-Syn mice subjected to cardiac arrest/cardiopulmonary resuscitation, 7.5% hypertonic saline treatment did not attenuate water content. Treatment with 7.5% hypertonic saline attenuated blood-brain barrier disruption at 24 hours following cardiac arrest/cardiopulmonary resuscitation in wild-type mice but not in alpha-Syn mice. Total aquaporin-4 protein expression was not different between 0.9% saline and hypertonic saline-treated wild-type mice. **CONCLUSIONS:** Following experimental cardiac arrest/cardiopulmonary resuscitation: 1) continuous hypertonic saline therapy maintained to achieve serum osmolality of approximately 350 mOsm/L is beneficial for the treatment of cerebral edema; 2) perivascular pool of aquaporin-4 plays a critical role in water egress from brain; and 3) hypertonic saline attenuates blood-brain barrier disruption via perivascular aquaporin-4 pool.

Nazemi, K. J., Shen, V., Finlay, J. L., Boyett, J., Kocak, M., Lafond, D., . . . Nicholson, H. S. (2016). **High Incidence of Venous Occlusive Disease With Myeloablative Chemotherapy Following Craniospinal Irradiation in Children With Newly Diagnosed High-Risk CNS Embryonal Tumors: A Report From the Children's Oncology Group (CCG-99702).** *Pediatr Blood Cancer*, 63(9), 1563-1570. doi:10.1002/pbc.26074

BACKGROUND: The outcomes with high-risk central nervous system (CNS) embryonal tumors remain relatively poor despite aggressive treatment. The purposes of this study using postirradiation myeloablative chemotherapy with autologous hematopoietic stem cell rescue (ASCR) were to document feasibility and describe toxicities of the regimen, establish the appropriate dose of thiotepa, and estimate the overall survival (OS) and event-free survival (EFS). **PROCEDURE:** The Children's Cancer Group conducted this pilot study in children and adolescents with CNS embryonal tumors. The treatment consisted of induction chemotherapy to mobilize hematopoietic stem cells, chemoradiotherapy, and myeloablative consolidation chemotherapy with ASCR. **RESULTS:** The study accrued 25 subjects in 40 months and was closed early due to toxicity, namely, venous occlusive disease (VOD) of the liver, more recently termed sinusoidal obstructive syndrome (SOS). Of 24

eligible subjects, three of 11 (27%) receiving thiotepa Dose Level 1 (150 mg/m²) /day x 3 days) and three of 12 (25%) receiving de-escalated Dose Level 0 (100 mg/m²) /day x 3 days) experienced VOD/SOS. One additional subject experienced toxic death attributed to septic shock; postmortem examination revealed clinically undiagnosed VOD/SOS. The 2-year EFS and OS were 54 +/- 10% and 71 +/- 9%, respectively. The 5-year EFS and OS were 46 +/- 11% and 50 +/- 11%. **CONCLUSIONS:** The treatment regimen was deemed to have an unacceptable rate of VOD/SOS. There was complete recovery in all six cases. The overall therapeutic strategy using a regimen less likely to cause VOD/SOS may merit further evaluation for the highest risk patients.

Neice, A. E., Larson, M. D., Behrends, M., & Bokoch, M. P. (2017). **In Response.** *Anesth Analg.* doi:10.1213/ane.0000000000002213

Newell, L. F., Holtan, S. G., Yates, J. E., Pereira, L., Tyner, J. W., Burd, I., & Bagby, G. C. (2017). **PIGF enhances TLR-dependent inflammatory responses in human mononuclear phagocytes.** *Am J Reprod Immunol.* doi:10.1111/aji.12709

PROBLEM: Levels of placental growth factor (PIGF) peak during third trimester of pregnancy, a time when women are at increased risk of virus-induced morbidity. We hypothesized PIGF might contribute to an exaggerated inflammatory response to Toll-like receptor (TLR) activation. **METHOD OF STUDY:** Primary human adult and cord blood CD14+ cells were cultured in the presence of TLR ligands and/or PIGF. **RESULTS:** PIGF significantly enhanced the magnitude and duration of TNF messenger RNA and protein production by TLR-7/8-activated monocytes, and increased subsequent production of TNF-independent inflammatory cytokines. This PIGF/TLR effect involved multiple inflammatory cytokines/chemokines and was seen with the majority of TLR agonists. PIGF enhanced phosphorylation of I κ B kinase (IKK) in monocytes stimulated with the TLR-7/8 agonist R848, and IKK inhibition completely suppressed the PIGF effect. **CONCLUSION:** PIGF enhances TLR-signaling upstream of IKK and contributes to an exaggerated pathologic pro-inflammatory state in response to activation of maternal and fetal mononuclear phagocytes by specific TLR agonists.

Newgard, C. D., Sanchez, B. J., Bulger, E. M., Brasel, K. J., Byers, A., Buick, J. E., . . . Schmicker, R. H. (2016). **A Geospatial Analysis of Severe Firearm Injuries Compared to Other Injury Mechanisms: Event Characteristics, Location, Timing, and Outcomes.** *Acad Emerg Med, 23*(5), 554-565. doi:10.1111/acem.12930

OBJECTIVES: Relatively little is known about the context and location of firearm injury events. Using a prospective cohort of trauma patients, we describe and compare severe firearm injury events to other violent and nonviolent injury mechanisms regarding incident location, proximity to home, time of day, spatial clustering, and outcomes. **METHODS:** This was a secondary analysis of a prospective cohort of injured children and adults with hypotension or Glasgow Coma Scale score \leq 8, injured by one of four primary injury mechanisms (firearm, stabbing, assault, and motor vehicle collision [MVC]) who were transported by emergency medical services to a Level I or II trauma center in 10 regions of the United States and Canada from January 1, 2010, through June 30, 2011. We used descriptive statistics and geospatial analyses to compare the injury groups, distance from home, outcomes, and spatial clustering. **RESULTS:** There were 2,079 persons available for analysis, including 506 (24.3%) firearm injuries, 297 (14.3%) stabbings, 339 (16.3%) assaults, and 950 (45.7%) MVCs. Firearm injuries resulted in the highest proportion of serious injuries (66.3%), early critical resources (75.3%), and in-hospital mortality (53.5%). Injury events occurring within 1 mile of a patient's home included 53.9% of stabbings, 49.2% of firearm events, 41.3% of assaults, and 20.0% of MVCs; the non-MVC events frequently occurred at home. While there was geospatial clustering, 94.4% of firearm events occurred outside of geographic clusters. **CONCLUSIONS:** Severe firearm events tend to occur within a patient's own neighborhood, often at home, and generally outside of geospatial clusters. Public health efforts should focus on the home in all types of neighborhoods to reduce firearm violence.

Nishida, M., Korzeniewska, A., Crone, N. E., Toyoda, G., Nakai, Y., Ofen, N., . . . Asano, E. (2017). **Brain network dynamics in the human articulatory loop**. *Clinical Neurophysiology*, 128(8), 1473-1487. doi:10.1016/j.clinph.2017.05.002

OBJECTIVE: The articulatory loop is a fundamental component of language function, involved in the short-term buffer of auditory information followed by its vocal reproduction. We characterized the network dynamics of the human articulatory loop, using invasive recording and stimulation. **METHODS:** We measured high-gamma activity 70-110 Hz recorded intracranially when patients with epilepsy either only listened to, or listened to and then reproduced two successive tones by humming. We also conducted network analyses, and analyzed behavioral responses to cortical stimulation. **RESULTS:** Presentation of the initial tone elicited high-gamma augmentation bilaterally in the superior-temporal gyrus (STG) within 40ms, and in the precentral and inferior-frontal gyri (PCG and IFG) within 160ms after sound onset. During presentation of the second tone, high-gamma augmentation was reduced in STG but enhanced in IFG. The task requiring tone reproduction further enhanced high-gamma augmentation in PCG during and after sound presentation. Event-related causality (ERC) analysis revealed dominant flows within STG immediately after sound onset, followed by reciprocal interactions involving PCG and IFG. Measurement of cortico-cortical evoked-potentials (CCEPs) confirmed connectivity between distant high-gamma sites in the articulatory loop. High-frequency stimulation of precentral high-gamma sites in either hemisphere induced speech arrest, inability to control vocalization, or forced vocalization. Vocalization of tones was accompanied by high-gamma augmentation over larger extents of PCG. **CONCLUSIONS:** Bilateral PCG rapidly and directly receives feed-forward signals from STG, and may promptly initiate motor planning including sub-vocal rehearsal for short-term buffering of auditory stimuli. Enhanced high-gamma augmentation in IFG during presentation of the second tone may reflect high-order processing of the tone sequence. **SIGNIFICANCE:** The articulatory loop employs sustained reciprocal propagation of neural activity across a network of cortical sites with strong neurophysiological connectivity.

Noyes, M. P., Ladermann, A., & Denard, P. J. (2017). **Functional Outcome and Healing of Large and Massive Rotator Cuff Tears Repaired With a Load-Sharing Rip-Stop Construct**. *Arthroscopy*. doi:10.1016/j.arthro.2017.04.003

PURPOSE: To prospectively review functional outcomes and healing rates of large and massive rotator cuff tears repaired with a load-sharing rip-stop (LSRS) technique. **METHODS:** Twenty-one consecutive patients underwent arthroscopic rotator cuff repair with an LSRS construct between January and December 2014. Seventeen patients with a minimum of 2 years' follow-up were included. Four patients did not complete clinical evaluations and functional outcome scores at a minimum of 2 years' follow-up and were lost to follow-up. Ultrasound imaging was used to assess for rotator cuff healing at a minimum of 6 months postoperatively. Range of motion, strength, and functional outcome scores were evaluated at final follow-up. **RESULTS:** Mean active forward elevation improved from 109 degrees preoperatively to 153 degrees postoperatively, and mean supraspinatus strength improved by 1 strength grade, from 3.5 preoperatively to 4.4 postoperatively. When we compared preoperative and postoperative values, the American Shoulder and Elbow Surgeons score improved from 40.8 to 89.5, the Single Assessment Numeric Evaluation score improved from 32.8 to 83.1, the Simple Shoulder Test score improved from 3.8 to 10.3, and the pain score on a visual analog scale decreased from 4.8 to 0.8 ($P < .001$). Of 17 patients, 13 (82%) were satisfied with their outcomes. Ultrasound evaluation 6 months after surgery showed complete healing in 53%, partial healing in 29%, and no healing in 18%. **CONCLUSIONS:** The LSRS construct showed satisfactory functional outcomes with reasonable healing rates in an otherwise challenging subset of rotator cuff tears. This construct may be an alternative for tears not amenable to double-row repair. **LEVEL OF EVIDENCE:** Level IV, therapeutic case series.

O'Glasser, A. Y., Taylor, C. C., & Hunter, A. J. (2017). **Beyond the algorithm: Implementation of a hospitalist-led pre-operative clinic assessment before cardiac surgery.** *Perioperative Care and Operating Room Management*, 8, 1-4. doi:10.1016/j.pcorn.2017.05.001

With the growth of dedicated pre-operative clinics in recent decades, patients have access to formalized and rigorous assessments in the days to weeks before surgery. The hallmark of pre-operative evaluations is cardiac risk stratification before non-cardiac surgery, yet any organ system has the potential to be addressed or further optimized before surgery. A formal, global clinic-based risk assessment before cardiac surgery seems to be a novel pre-operative clinic practice pattern, especially for a hospitalist-led preoperative medicine clinic. In July 2014, the Pre-Operative Medicine Clinic (PMC) within the Division of Hospital Medicine at Oregon Health & Science University began to formally assess patients before cardiac surgery. Here, we aim to describe our first year's experience with this patient population and report on its efficacy and practicality. © 2017 Elsevier Inc.

Othman, R. A., Myrie, S. B., Mymin, D., Roulet, J. B., DeBarber, A. E., Steiner, R. D., & Jones, P. J. H. (2017). **Thyroid Hormone Status in Sitosterolemia Is Modified by Ezetimibe.** *J Pediatr*. doi:10.1016/j.jpeds.2017.05.049

OBJECTIVES: To assess the association between biomarkers of thyroid status and 5alpha-stanols in patients with sitosterolemia treated with ezetimibe (EZE). **STUDY DESIGN:** Eight patients with sitosterolemia (16-56 years of age) were studied during 14 weeks off EZE therapy and 14 weeks on EZE (10 mg/day). Serum thyroid biomarkers (free triiodothyronine [FT3], free thyroxine [FT4], FT3/FT4 ratio, thyroid-stimulating hormone), 5alpha-stanols (sitostanol and cholestanol), and cholestanol precursors (total cholesterol and its synthesis marker lathosterol, and 7alpha-hydroxy-4-cholesten-3-one cholestanol) were measured at baseline and during the 14 weeks off EZE and on EZE. **RESULTS:** EZE increased FT3/FT4 (10% +/- 4%; P = .02). EZE reduced plasma and red blood cells sitostanol (-38% +/- 6% and -20% +/- 4%; all P < .05) and cholestanol (-18% +/- 6% and -13% +/- 3%; all P < .05). The change in plasma cholestanol level on EZE inversely correlated with the change in FT3/FT4 (r = -0.86; P = .01). EZE lowered total cholesterol (P < .0001) and did not affect 7alpha-hydroxy-4-cholesten-3-one cholestanol. EZE increased (P < .0001) lathosterol initially, but the level was not sustained, resulting in similar levels at week 14 off EZE and on EZE. **CONCLUSION:** In patients with STSL, 5alpha-stanols levels might be associated with thyroid function. EZE reduces circulating 5alpha-stanols while increasing FT3/FT4, implying increased conversion of T4 to T3, thus possibly improving thyroid hormone status. **TRIAL REGISTRATION:** ClinicalTrials.govNCT01584206.

Paddock, M., Grock, A., DeLoughery, T., & Mason, J. (2017). **Can Neutropenic Fever Ever Be Low Risk?** *Ann Emerg Med*, 69(6), 765-767. doi:10.1016/j.annemergmed.2017.03.068

Pannucci, C. J., Obi, A. T., Timmins, B. H., & Cochran, A. L. (2017). **Venous Thromboembolism in Patients with Thermal Injury: A Review of Risk Assessment Tools and Current Knowledge on the Effectiveness and Risks of Mechanical and Chemical Prophylaxis.** *Clinics in Plastic Surgery*, 44(3), 573-581. doi:10.1016/j.cps.2017.02.002

Venous thromboembolism (VTE) can be a life-threatening or limb-threatening complication of thermal injury. The severity of burn injury can be used to predict VTE risk among patients with thermal injury, and a weighted risk-stratification tool has been developed. This article reviews the incidence, diagnosis, and management of thromboembolic events in patients with burns. The article particularly focuses on identifying those patients who are at highest risk for VTE and provides recommendations on mechanical and chemical prophylaxis. © 2017 Elsevier Inc.

Papak, J., & Chiovaro, J. (2017). **Capsule Commentary on Blumenthal et al., Using a Self-Reported Global Health Measure to Identify Patients at High Risk for Future Healthcare Utilization.** *J Gen Intern Med.* doi:10.1007/s11606-017-4076-0

Passias, P. G., Oh, C., Jalai, C. M., Worley, N., Lafage, R., Scheer, J. K., . . . Ames, C. P. (2016). **Predictive Model for Cervical Alignment and Malalignment Following Surgical Correction of Adult Spinal Deformity.** *Spine (Phila Pa 1976)*, 41(18), E1096-1103. doi:10.1097/brs.0000000000001640

STUDY DESIGN: Retrospective review of prospective multicenter database. OBJECTIVE: Use predictive modeling to identify patient characteristics, radiographic, and surgical variables that predict reaching an outcome threshold of suboptimal cervical alignment after adult spinal deformity (ASD) surgery. SUMMARY OF BACKGROUND DATA: Cervical deformity (CD) after ASD correction has been defined with the following criteria: T1S-CL > 20 degrees, C2-C7 SVA > 40 mm, and/or C2-C7 kyphosis > 10 degrees. While studies have analyzed CD predictors, few have defined and identified predictors of optimal cervical alignment after thoracolumbar surgery. METHODS: Inclusion criteria were surgical ASD patients with baseline and 2-year follow-up. Postoperative cervical alignment (CA) and malalignment (nonCA) at 2 years was defined with the following radiographic criteria: 0 degrees \leq T1S-CL \leq 20 degrees, 0 mm \leq C2-C7 SVA \leq 40 mm, or C2-C7 lordosis > 0 degrees. Three thresholds classifying malalignment were defined: (T1) missing 1 criterion, (T2) missing 2 criteria, (T3) missing 3 criteria. Multivariable logistic stepwise regression models with bootstrap resampling procedure were performed for demographic, surgical, and radiographic variables. The model was validated with receiver operative characteristic and area under the curve. RESULTS: Two hundred twenty-five surgical ASD patients were included. At 2 years 208 patients (92.4%) were grouped as CA in T3, while 17 (7.6%) were nonCA. Patients were similar in age (CA: 56.10 vs. nonCA: 55.78 years, $P = 0.150$), BMI (CA: 26.93 vs. nonCA: 26.94 kg/m, $P = 0.716$), and sex (CA: 76.5% vs. nonCA: 87.0%, $P = 0.194$). The final predictive model included C2 slope, C2-T3 CL, T1S-CL, C2-C7 CL, Pelvic Tilt, C2-S1 SVA, PI-LL, and Smith-Peterson osteotomies number. In this model (area under the curve 89.22% [97.49-80.96%]), the following variables were identified as predictors of nonCA: increased Smith-Peterson osteotomies use (OR: 1.336, $P = 0.017$), and C2-T3 angle (OR: 1.048, $P = 0.005$). CONCLUSION: This study created a statistical model that predicts poor 2-year postoperative cervical malalignment in ASD patients. T3 (patients not meeting all three alignment criteria) was the most effective threshold for modeling nonCA, and included increased baseline C2-T3 angle and increased Smith-Peterson osteotomies during index. LEVEL OF EVIDENCE: 3.

Patel, U. A., Hernandez, D., Shnayder, Y., Wax, M. K., Hanasono, M. M., Hornig, J., . . . Richmon, J. M. (2017). **Free Flap Reconstruction Monitoring Techniques and Frequency in the Era of Restricted Resident Work Hours.** *JAMA Otolaryngol Head Neck Surg.* doi:10.1001/jamaoto.2017.0304

Importance: Free flap reconstruction of the head and neck is routinely performed with success rates around 94% to 99% at most institutions. Despite experience and meticulous technique, there is a small but recognized risk of partial or total flap loss in the postoperative setting. Historically, most microvascular surgeons involve resident house staff in flap monitoring protocols, and programs relied heavily on in-house resident physicians to assure timely intervention for compromised flaps. In 2003, the Accreditation Council for Graduate Medical Education mandated the reduction in the hours a resident could work within a given week. At many institutions this new era of restricted resident duty hours reshaped the protocols used for flap monitoring to adapt to a system with reduced resident labor. Objectives: To characterize various techniques and frequencies of free flap monitoring by nurses and resident physicians; and to determine if adapted resident monitoring frequency is associated with flap compromise and outcome. Design, Setting, and Participants: This multi-institutional retrospective review included patients undergoing free flap reconstruction to the head and/or neck between January 2005 and January 2015. Consecutive patients were included from different academic institutions or tertiary referral centers to reflect evolving practices. Main Outcomes and Measures: Technique, frequency, and personnel for flap monitoring; flap complications; and flap success. Results: Overall, 1085 patients (343 women [32%] and 742 men [78%]) from 9 institutions were

included. Most patients were placed in the intensive care unit postoperatively (n = 790 [73%]), while the remaining were placed in intermediate care (n = 201 [19%]) or in the surgical ward (n = 94 [7%]). Nurses monitored flaps every hour (q1h) for all patients. Frequency of resident monitoring varied, with 635 patients monitored every 4 hours (q4h), 146 monitored every 8 hours (q8h), and 304 monitored every 12 hours (q12h). Monitoring techniques included physical examination (n = 949 [87%]), handheld external Doppler sonography (n = 739 [68%]), implanted Doppler sonography (n = 333 [31%]), and needle stick (n = 349 [32%]); 105 patients (10%) demonstrated flap compromise, prompting return to the operating room in 96 patients. Of these 96 patients, 46 had complete flap salvage, 22 had partial loss, and 37 had complete loss. The frequency of resident flap checks did not affect the total flap loss rate (q4h, 25 patients [4%]; q8h, 8 patients [6%]; and q12h, 8 patients [3%]). Flap salvage rates for compromised flaps were not statistically different. Conclusions and Relevance: Academic centers rely primarily on q1h flap checks by intensive care unit nurses using physical examination and Doppler sonography. Reduced resident monitoring frequency did not alter flap salvage nor flap outcome. These findings suggest that institutions may successfully monitor free flaps with decreased resident burden.

Paterson, E. K., & Courtneidge, S. A. (2017). **Invadosomes are coming: new insights into function and disease relevance.** *Febs j.* doi:10.1111/febs.14123

Invadopodia and podosomes are discrete, actin-based molecular protrusions that form in cancer cells and normal cells, respectively, in response to diverse signaling pathways and extracellular matrix cues. Although they participate in a host of different cellular processes, they share a common functional theme of controlling pericellular proteolytic activity, which sets them apart from other structures that function in migration and adhesion, including focal adhesions, lamellipodia, and filopodia. In this review, we highlight research that explores the function of these complex structures, including roles for podosomes in embryonic and postnatal development, in angiogenesis and remodeling of the vasculature, in maturation of the postsynaptic membrane, in antigen sampling and recognition, and in cell-cell fusion mechanisms, as well as the involvement of invadopodia at multiple steps of the metastatic cascade, and how all of this may apply in the treatment of human disease states. Finally, we explore recent research that implicates a novel role for exosomes and microvesicles in invadopodia-dependent and invadopodia-independent mechanisms of invasion, respectively.

Peterson, D. S., King, L. A., Cohen, R. G., & Horak, F. B. (2016). **Cognitive Contributions to Freezing of Gait in Parkinson Disease: Implications for Physical Rehabilitation.** *Physical Therapy, 96*(5), 659-670. doi:10.2522/ptj.20140603

People with Parkinson disease (PD) who show freezing of gait also have dysfunction in cognitive domains that interact with mobility. Specifically, freezing of gait is associated with executive dysfunction involving response inhibition, divided attention or switching attention, and visuospatial function. The neural control impairments leading to freezing of gait have recently been attributed to higher-level, executive and attentional cortical processes involved in coordinating posture and gait rather than to lower-level, sensorimotor impairments. To date, rehabilitation for freezing of gait primarily has focused on compensatory mobility training to overcome freezing events, such as sensory cueing and voluntary step planning. Recently, a few interventions have focused on restitutive, rather than compensatory, therapy. Given the documented impairments in executive function specific to patients with PD who freeze and increasing evidence of overlap between cognitive and motor function, incorporating cognitive challenges with mobility training may have important benefits for patients with freezing of gait. Thus, a novel theoretical framework is proposed for exercise interventions that jointly address both the specific cognitive and mobility challenges of people with PD who freeze.

Pham, T. H., Melton, S. D., McLaren, P. J., Mokdad, A. A., Huerta, S., Wang, D. H., . . . Dolan, J. P. (2017). **Laparoscopic ischemic conditioning of the stomach increases neovascularization of the gastric conduit in patients undergoing esophagectomy for cancer.** *J Surg Oncol.* doi:10.1002/jso.24668

BACKGROUND AND OBJECTIVES: Gastric ischemic preconditioning has been proposed to improve blood flow and reduce the incidence of anastomotic complications following esophagectomy with gastric pull-up. This study aimed to evaluate the effect of prolonged ischemic preconditioning on the degree of neovascularization in the distal gastric conduit at the time of esophagectomy. **METHODS:** A retrospective review of a prospectively maintained database identified 30 patients who underwent esophagectomy. The patients were divided into three groups: control (no preconditioning, n = 9), partial (short gastric vessel ligation only, n = 8), and complete ischemic preconditioning (left and short gastric vessel ligation, n = 13). Microvessel counts were assessed, using immunohistologic analysis to determine the degree of neovascularization at the distal gastric margin. **RESULTS:** The groups did not differ in age, gender, BMI, pathologic stage, or cancer subtype. Ischemic preconditioning durations were 163 +/- 156 days for partial ischemic preconditioning, compared to 95 +/- 50 days for complete ischemic preconditioning (P = 0.2). Immunohistologic analysis demonstrated an increase in microvessel counts of 29% following partial ischemic preconditioning (P = 0.3) and 67% after complete ischemic preconditioning (P < 0.0001), compared to controls. **CONCLUSIONS:** Our study indicates that prolonged ischemic preconditioning is safe and does not interfere with subsequent esophagectomy. Complete ischemic preconditioning increased neovascularization in the distal gastric conduit.

Pianko, M. J., Funt, S. A., Page, D. B., Cattry, D., Scott, E. C., Ansell, S. M., . . . Lesokhin, A. M. (2017). **Efficacy and toxicity of therapy immediately after treatment with nivolumab in relapsed multiple myeloma.** *Leukemia and Lymphoma*, 1-4. doi:10.1080/10428194.2017.1320713

Pines, A. R., Alghoul, M. S., Hamade, Y. J., Sattur, M. G., Aoun, R. J. N., Halasa, T. K., . . . Bendok, B. R. (2017). **Assessment of the interrater reliability of the congress of neurological surgeons microanastomosis assessment scale.** *Operative Neurosurgery*, 13(1), 108-112. doi:10.1227/NEU.0000000000001403

BACKGROUND: The potential for simulation-based learning in neurosurgical training has led the Congress of Neurosurgical Surgeons to develop a series of simulation modules. The Northwestern Objective Microanastomosis Assessment Tool (NOMAT) was created as the corresponding assessment tool for the Congress of Neurosurgical Surgeons Microanastomosis Module. The face and construct validity of the NOMAT have been previously established. **OBJECTIVE:** To further validate the NOMAT by determining its interrater reliability (IRR) between raters of varying levels of microsurgical expertise. **METHODS:** The NOMAT was used to assess residents' performance in a microanastomosis simulation module in 2 settings: Northwestern University and the Society of Neurological Surgeons 2014 Boot Camp at the University of Indiana. At Northwestern University, participants were scored by 2 experienced microsurgeons. At the University of Indiana, participants were scored by 2 postdoctoral fellows and an experienced microsurgeon. The IRR of NOMAT was estimated by computing the intraclass correlation coefficient using SPSS v22.0 (IBM, Armonk, New York). **RESULTS:** A total of 75 residents were assessed. At Northwestern University, 21 residents each performed microanastomosis on 2 model vessels of different sizes, one 3 mm and one 1 mm. At the University of Indiana, 54 residents performed a single microanastomosis procedure on 3-mm vessels. The intraclass correlation coefficient of the total NOMAT scores was 0.88 at Northwestern University and 0.78 at the University of Indiana. **CONCLUSION:** This study indicates high IRR for the NOMAT. These results suggest that the use of raters with varying levels of expertise does not compromise the precision or validity of the scale. This allows for a wider adoption of the scale and, hence, a greater potential educational impact. Copyright © 2016 by the Congress of Neurological Surgeons.

Price, J. R., Guran, L. A., Gregory, W. T., & McDonagh, M. S. (2016). **Nitrofurantoin vs other prophylactic agents in reducing recurrent urinary tract infections in adult women: a systematic review and meta-analysis.** *American Journal of Obstetrics and Gynecology*, 215(5), 548-560. doi:10.1016/j.ajog.2016.07.040

BACKGROUND: The clinical and financial burden from bladder infections is significant. Daily antibiotic use is the recommended strategy for recurrent urinary tract infection prevention. Increasing antibiotic resistance rates, however, require immediate identification of innovative alternative prophylactic therapies. This systematic review aims to provide guidance on gaps in evidence to guide future research. **OBJECTIVE:** The objective of this review was to provide current pooled estimates of randomized control trials comparing the effects of nitrofurantoin vs other agents in reducing recurrent urinary tract infections in adult, nonpregnant women and assess relative adverse side effects. **DATA SOURCES:** Data sources included the following: MEDLINE, Jan. 1, 1946, to Jan. 31, 2015; Cochrane Central Register of Controlled Trials the Cochrane Database of Systematic Reviews, and web sites of the National Institute for Clinical Excellence, and the National Guideline Clearinghouse from 2000 to 2015. Randomized control trials of women with recurrent urinary tract infections comparing nitrofurantoin with any other treatment were included. **STUDY DESIGN:** A protocol for the study was developed a priori. Published guidance was followed for assessment of study quality. All meta-analyses were performed using random-effects models with Stats Direct Software. Dual review was used for all decisions and data abstraction. **RESULTS:** Twelve randomized control trials involving 1063 patients were included. One study that had a serious flaw was rated poor in quality, one study rated good, and the remainder fair. No significant differences in prophylactic antibiotic treatment with nitrofurantoin and norfloxacin, trimethoprim, sulfamethoxazole/trimethoprim, methamine hippurate, estriol, or cefaclor were found in clinical or microbiological cure in adult nonpregnant women with recurrent urinary tract infections (9 randomized control trials, 673 patients, relative risk ratio, 1.06; 95% confidence interval, 0.89-1.27; I², 65%; and 12 randomized control trials, 1063 patients, relative risk ratio, 1.06; 95% confidence interval, 0.90-1.26; I², 76%, respectively). Duration of prophylaxis also did not have a significant impact on outcomes. There was a statistically significant difference in overall adverse effects, with nitrofurantoin resulting in greater risk than other prophylactic treatments (10 randomized control trials, 948 patients, relative risk ratio, 2.17; 95% confidence interval, 1.34-3.50; I², 61%). Overall, the majority of nitrofurantoin adverse effects were gastrointestinal, with a significant difference for withdrawals (12 randomized control trials, 1063 patients, relative risk ratio, 2.14; 95% confidence interval, 1.28-3.56; I², 8%). **CONCLUSION:** Nitrofurantoin had similar efficacy but a greater risk of adverse events than other prophylactic treatments. Balancing the risks of adverse events, particularly gastrointestinal symptoms, with potential benefits of decreasing collateral ecological damage should be considered if selecting nitrofurantoin.

Pusateri, A. E., Given, M. B., Schreiber, M. A., Spinella, P. C., Pati, S., Kozar, R. A., . . . Cap, A. P. (2016). **Dried plasma: state of the science and recent developments.** *Transfusion*, *56 Suppl 2*, S128-139. doi:10.1111/trf.13580

The early transfusion of plasma is important to ensure optimal survival of patients with traumatic hemorrhage. In military and remote or austere civilian settings, it may be impossible to move patients to hospital facilities within the first few hours of injury. A dried plasma product with reduced logistical requirements is needed to enable plasma transfusion where medically needed, instead of only where freezers and other equipment are available. First developed in the 1930s, pooled lyophilized plasma was widely used by British and American forces in WWII and the Korean War. Historical dried plasma products solved the logistical problem but were abandoned because of disease transmission. Modern methods to improve blood safety have made it possible to produce safe and effective dried plasma. Dried plasma products are available in France, Germany, South Africa, and a limited number of other countries. However, no product is available in the US. Promising products are in development that employ different methods of drying, pathogen reduction, pooling, packaging, and other approaches. Although challenges exist, the in vitro and in vivo data suggest that these products have great potential to be safe and effective. The history, state of the science, and recent developments in dried plasma are reviewed.

Ramsey, S. D., Nademanee, A., Masszi, T., Holowiecki, J., Abidi, M., Chen, A., . . . Moskowitz, C. H. (2016). **Quality of life results from a phase 3 study of brentuximab vedotin consolidation following autologous haematopoietic stem cell transplant for persons with Hodgkin lymphoma.** *British Journal of Haematology*, *175*(5), 860-867. doi:10.1111/bjh.14316

Brentuximab vedotin (BV) significantly improved progression-free survival in a phase 3 study in patients with relapsed or refractory Hodgkin lymphoma (RR-HL) post-autologous-haematopoietic stem cell transplant (auto-HSCT); we report the impact of BV on quality of life (QOL) from this trial. The European Quality of Life five dimensions questionnaire was administered at the beginning of each cycle, end of treatment, and every 3 months during follow-up; index value scores were calculated using the time trade-off (TTO) method for UK-weighted value sets. Questionnaire adherence during the trial was 87.5% (N = 329). In an intent-to-treat analysis, compared with placebo, TTO scores in the BV arm did not exceed the minimally important difference (MID) of 0.08 except at month 15 (-0.084; 95% confidence interval, -0.143 to -0.025). On-treatment index scores were similar between arms and did not reach the MID at any time point; mixed-effect modelling showed that BV treatment effect was not significant (P = 0.2127). BV-associated peripheral neuropathy did not meaningfully impact QOL. Utility scores for patients who progressed declined compared with those who did not; TTO scores between these patients exceeded the MID beginning at month 15. In conclusion, QOL decreased modestly with BV consolidation treatment in patients with RR-HL at high risk of relapse after auto-HSCT.

Ramyar, M., Leary, C., Raja, A., Butler, A. P. H., Woodfield, T. B. F., & Anderson, N. G. (2017). *Establishing a method to measure bone structure using spectral CT*.

Combining bone structure and density measurement in 3D is required to assess site-specific fracture risk. Spectral molecular imaging can measure bone structure in relation to bone density by measuring macro and microstructure of bone in 3D. This study aimed to optimize spectral CT methodology to measure bone structure in excised bone samples. MARS CT with CdTe Medipix3RX detector was used in multiple energy bins to calibrate bone structure measurements. To calibrate thickness measurement, eight different thicknesses of Aluminium (Al) sheets were scanned one in air and the other around a falcon tube and then analysed. To test if trabecular thickness measurements differed depending on scan plane, a bone sample from sheep proximal tibia was scanned in two orthogonal directions. To assess the effect of air on thickness measurement, two parts of the same human femoral head were scanned in two conditions (in the air and in PBS). The results showed that the MARS scanner (with 90µm voxel size) is able to accurately measure the Al (in air) thicknesses over 200µm but it underestimates the thicknesses below 200µm because of partial volume effect in Al-air interface. The Al thickness measured in the highest energy bin is overestimated at Al-falcon tube interface. Bone scanning in two orthogonal directions gives the same trabecular thickness and air in the bone structure reduced measurement accuracy. We have established a bone structure assessment protocol on MARS scanner. The next step is to combine this with bone densitometry to assess bone strength. © 2017 SPIE.

Rastegar, F., Contag, A., Daniels, A., Hiratzka, J., Lin, C., Chang, J., . . . Hart, R. (2017). **Proximal Junctional Kyphosis: Inter- and Intra-observer Reliability of Radiographic Measurements in Adult Spinal Deformity**. *Spine*. doi:10.1097/BRS.0000000000002261

STUDY DESIGN.: Reliability study of radiographic measures of proximal junctional kyphosis in adult spinal deformity patients. OBJECTIVE.: Assess impacts of level of proximal endpoint and vertebral fracture on reliability of measurement of junctional kyphosis. SUMMARY OF BACKGROUND DATA.: Radiographic assessment is important in determining management of patients with Proximal Junctional Kyphosis (PJK) or Proximal Junctional Failure (PJF). No study to date has evaluated the reliability of radiographic measurement of the junctional kyphotic angle after surgery for Adult Spinal Deformity (ASD). METHODS.: Post-operative radiographs from 52 ASD patients were divided into four categories based on the level of the upper instrumented vertebra (UIV) and the presence or absence of PJF: upper thoracic without failure (UT), thoracolumbar without failure (TL), upper thoracic with PJF (UTF) and thoracolumbar with PJF (TLF). Nine surgeon reviewers performed radiographic measurements of kyphosis between UIV+2 and UIV twice at least 4-weeks apart. Intraclass correlation coefficients (ICC) were calculated to determine inter- and intra-observer reliability. RESULTS.: Inter-observer reliability for measurements of UT, TL, UTF, TLF were all "almost perfect" with ICC scores of 0.917, 0.965, 0.956, 0.882, and 0.932, 0.975, 0.958, 0.989, for sessions 1 and 2 respectively.

Similarly, ICC's for kyphosis measurements for the TL and TLF group had "almost perfect" agreement with means of 0.898 (range: 0.817–0.969) and 0.976 (range: 0.931–0.995), respectively. ICC's for measurements for the UT and UTF groups all had "substantial" or "almost perfect" agreement with means of 0.801 (range: 0.662–0.942) and 0.879 (range: 0.760–0.988), respectively. CONCLUSION.: This study demonstrates high inter- and intra-observer reliability of proximal junctional kyphosis measurement following instrumented fusion for ASD, independent of the presence or absence of PJF. Although slightly lower for upper thoracic than for thoracolumbar proximal endpoints, all ICC's consistently reached at least "substantial agreement" and "near perfect agreement" for most. Level of Evidence: 4 Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

Rex, D. K., Boland, C. R., Dominitz, J. A., Giardiello, F. M., Johnson, D. A., Kaltenbach, T., . . . Robertson, D. J. (2017). **Colorectal Cancer Screening: Recommendations for Physicians and Patients From the U.S. Multi-Society Task Force on Colorectal Cancer.** *Gastroenterology*. doi:10.1053/j.gastro.2017.05.013

This document updates the colorectal cancer (CRC) screening recommendations of the U.S. Multi-Society Task Force of Colorectal Cancer (MSTF), which represents the American College of Gastroenterology, the American Gastroenterological Association, and The American Society for Gastrointestinal Endoscopy. CRC screening tests are ranked in 3 tiers based on performance features, costs, and practical considerations. The first-tier tests are colonoscopy every 10 years and annual fecal immunochemical test (FIT). Colonoscopy and FIT are recommended as the cornerstones of screening regardless of how screening is offered. Thus, in a sequential approach based on colonoscopy offered first, FIT should be offered to patients who decline colonoscopy. Colonoscopy and FIT are recommended as tests of choice when multiple options are presented as alternatives. A risk-stratified approach is also appropriate, with FIT screening in populations with an estimated low prevalence of advanced neoplasia and colonoscopy screening in high prevalence populations. The second-tier tests include CT colonography every 5 years, the FIT-fecal DNA test every 3 years, and flexible sigmoidoscopy every 5 to 10 years. These tests are appropriate screening tests, but each has disadvantages relative to the tier 1 tests. Because of limited evidence and current obstacles to use, capsule colonoscopy every 5 years is a third-tier test. We suggest that the Septin9 serum assay (Epigenomics, Seattle, Wash) not be used for screening. Screening should begin at age 50 years in average-risk persons, except in African Americans in whom limited evidence supports screening at 45 years. CRC incidence is rising in persons under age 50, and thorough diagnostic evaluation of young persons with suspected colorectal bleeding is recommended. Discontinuation of screening should be considered when persons up to date with screening, who have prior negative screening (particularly colonoscopy), reach age 75 or have <10 years of life expectancy. Persons without prior screening should be considered for screening up to age 85, depending on age and comorbidities. Persons with a family history of CRC or a documented advanced adenoma in a first-degree relative age <60 years or 2 first-degree relatives with these findings at any age are recommended to undergo screening by colonoscopy every 5 years, beginning 10 years before the age at diagnosis of the youngest affected relative or age 40, whichever is earlier. Persons with a single first-degree relative diagnosed at ≥60 years with CRC or an advanced adenoma can be offered average-risk screening options beginning at age 40 years. © 2017 AGA Institute, American College of Gastroenterology, and the American Society for Gastrointestinal Endoscopy.

Rex, D. K., Boland, C. R., Dominitz, J. A., Giardiello, F. M., Johnson, D. A., Kaltenbach, T., . . . Robertson, D. J. (2017). **Colorectal cancer screening: Recommendations for physicians and patients from the U.S. Multi-Society Task Force on Colorectal Cancer.** *Gastrointestinal Endoscopy*, 86(1), 18-33. doi:10.1016/j.gie.2017.04.003

Rex, D. K., Boland, C. R., Dominitz, J. A., Giardiello, F. M., Johnson, D. A., Kaltenbach, T., . . . Robertson, D. J. (2017). **Colorectal Cancer Screening: Recommendations for Physicians and Patients from the U.S. Multi-Society Task Force on Colorectal Cancer.** *Am J Gastroenterol*. doi:10.1038/ajg.2017.174

This document updates the colorectal cancer (CRC) screening recommendations of the U.S. Multi-Society Task Force of Colorectal Cancer (MSTF), which represents the American College of Gastroenterology, the American Gastroenterological Association, and The American Society for Gastrointestinal Endoscopy. CRC screening tests are ranked in 3 tiers based on performance features, costs, and practical considerations. The first-tier tests are colonoscopy every 10 years and annual fecal immunochemical test (FIT). Colonoscopy and FIT are recommended as the cornerstones of screening regardless of how screening is offered. Thus, in a sequential approach based on colonoscopy offered first, FIT should be offered to patients who decline colonoscopy. Colonoscopy and FIT are recommended as tests of choice when multiple options are presented as alternatives. A risk-stratified approach is also appropriate, with FIT screening in populations with an estimated low prevalence of advanced neoplasia and colonoscopy screening in high prevalence populations. The second-tier tests include CT colonography every 5 years, the FIT-fecal DNA test every 3 years, and flexible sigmoidoscopy every 5 to 10 years. These tests are appropriate screening tests, but each has disadvantages relative to the tier 1 tests. Because of limited evidence and current obstacles to use, capsule colonoscopy every 5 years is a third-tier test. We suggest that the Septin9 serum assay (Epigenomics, Seattle, Wash) not be used for screening. Screening should begin at age 50 years in average-risk persons, except in African Americans in whom limited evidence supports screening at 45 years. CRC incidence is rising in persons under age 50, and thorough diagnostic evaluation of young persons with suspected colorectal bleeding is recommended. Discontinuation of screening should be considered when persons up to date with screening, who have prior negative screening (particularly colonoscopy), reach age 75 or have <10 years of life expectancy. Persons without prior screening should be considered for screening up to age 85, depending on age and comorbidities. Persons with a family history of CRC or a documented advanced adenoma in a first-degree relative age <60 years or 2 first-degree relatives with these findings at any age are recommended to undergo screening by colonoscopy every 5 years, beginning 10 years before the age at diagnosis of the youngest affected relative or age 40, whichever is earlier. Persons with a single first-degree relative diagnosed at ≥ 60 years with CRC or an advanced adenoma can be offered average-risk screening options beginning at age 40 years. *Am J Gastroenterol* advance online publication, 6 June 2017; doi:10.1038/ajg.2017.174.

Riddle, M. C. (2017). **Modern sulfonylureas: Dangerous or wrongly accused?** *Diabetes Care*, 40(5), 629-631. doi:10.2337/dci17-0003

Rieckmann, T., Renfro, S., McCarty, D., Baker, R., & McConnell, K. J. (2017). **Quality Metrics and Systems Transformation: Are We Advancing Alcohol and Drug Screening in Primary Care?** *Health Services Research*. doi:10.1111/1475-6773.12716

OBJECTIVE: To examine the influence of Oregon's coordinated care organizations (CCOs) and pay-for-performance incentive model on completion of screening and brief intervention (SBI) and utilization of substance use disorder (SUD) treatment services. **DATA SOURCES/STUDY SETTING:** Secondary analysis of Medicaid encounter data from 2012 to 2015 and semiannual qualitative interviews with stakeholders in CCOs. **STUDY DESIGN:** Longitudinal mixed-methods design with simultaneous data collection with equal importance. **DATA COLLECTION/EXTRACTION METHODS:** Qualitative interviews were recorded, transcribed, and coded in ATLAS.ti. Quantitative data included Medicaid encounters 30 months prior to CCO implementation, a 6-month transition period, and 30 months following CCO implementation. Data were aggregated by half-year with analyses restricted to Medicaid recipients 18-64 years of age enrolled in a CCO, not eligible for Medicare coverage or Medicaid expansion. **PRINCIPAL FINDINGS:** Quantitative analysis documented a significant increase in SBI rates coinciding with CCO implementation (0.1 to 4.6 percent). Completed SBI was not associated with increased initiation in treatment for SUD diagnoses. Qualitative analysis highlighted importance of aligning incentives, workflow redesign, and leadership to facilitate statewide SBI. **CONCLUSIONS:** Results provide modest support for use of a performance metric to expand SBI in primary

care. Future research should examine health reform efforts that increase initiation and engagement in SUD treatment.

Rilinger, J. F., Smith, C. M., deRegnier, R. A. O., Goldstein, J. L., Mills, M. G., Reynolds, M., . . . Wainwright, M. S. (2016). **Transcranial Doppler Identification of Neurologic Injury during Pediatric Extracorporeal Membrane Oxygenation Therapy.** *Journal of Stroke and Cerebrovascular Diseases*. doi:10.1016/j.jstrokecerebrovasdis.2017.05.022

Background: We used transcranial Doppler to examine changes in cerebral blood flow velocity in children treated with extracorporeal membrane oxygenation. We examined the association between those changes and radiologic, electroencephalographic, and clinical evidence of neurologic injury. Methods: This was a retrospective review and prospective observational study of patients 18 years old and younger at a single university children's hospital. Transcranial Doppler studies were obtained every other day during the first 7 days of extracorporeal membrane oxygenation, and 1 additional study following decannulation, in conjunction with serial neurologic examinations, brain imaging, and 6- to 12-month follow-up. Results: The study included 27 patients, the majority (26) receiving veno-arterial extracorporeal membrane oxygenation. Transcranial Doppler velocities during extracorporeal membrane oxygenation were significantly lower than published values for age-matched healthy and critically ill children across different cerebral arteries. Neonates younger than 10 days had higher velocities than expected. Blood flow velocity increased after extracorporeal membrane oxygenation decannulation and was comparable with age-matched critically ill children. There was no significant association between velocity measurements of individual arteries and acute neurologic injury as defined by either abnormal neurologic examination, seizures during admission, or poor pediatric cerebral performance category. However, case analysis identified several patients with regional and global increases in velocities that corresponded to neurologic injury including stroke and seizures. Conclusions: Cerebral blood flow velocities during extracorporeal membrane oxygenation deviate from age-specific normal values in all major cerebral vessels and across different age groups. Global or regional elevations and asymmetries in flow velocity may suggest impending neurologic injury. © 2017 National Stroke Association.

Robertson, D. J., Lee, J. K., Boland, C. R., Dominitz, J. A., Giardiello, F. M., Johnson, D. A., . . . Rex, D. K. (2017). **Recommendations on Fecal Immunochemical Testing to Screen for Colorectal Neoplasia: A Consensus Statement by the US Multi-Society Task Force on Colorectal Cancer.** *Am J Gastroenterol*, 112(1), 37-53. doi:10.1038/ajg.2016.492

The use of the fecal occult blood test (FOBT) for colorectal cancer (CRC) screening is supported by randomized trials demonstrating effectiveness in cancer prevention and widely recommended by guidelines for this purpose. The fecal immunochemical test (FIT), as a direct measure of human hemoglobin in stool has a number of advantages relative to conventional FOBT and is increasingly used relative to that test. This review summarizes current evidence for FIT in colorectal neoplasia detection and the comparative effectiveness of FIT relative to other commonly used CRC screening modalities. Based on evidence, guidance statements on FIT application were developed and quality metrics for program implementation proposed.

Robinson-Cohen, C., Lutsey, P. L., Kleber, M. E., Nielson, C. M., Mitchell, B. D., Bis, J. C., . . . Kestenbaum, B. (2017). **Genetic Variants Associated with Circulating Parathyroid Hormone.** *J Am Soc Nephrol*, 28(5), 1553-1565. doi:10.1681/asn.2016010069

Parathyroid hormone (PTH) is a primary calcium regulatory hormone. Elevated serum PTH concentrations in primary and secondary hyperparathyroidism have been associated with bone disease, hypertension, and in some studies, cardiovascular mortality. Genetic causes of variation in circulating PTH concentrations are incompletely understood. We performed a genome-wide association study of serum PTH concentrations among 29,155 participants of European ancestry from 13 cohort studies (n=22,653 and n=6502 in discovery

and replication analyses, respectively). We evaluated the association of single nucleotide polymorphisms (SNPs) with natural log-transformed PTH concentration adjusted for age, sex, season, study site, and principal components of ancestry. We discovered associations of SNPs from five independent regions with serum PTH concentration, including the strongest association with rs6127099 upstream of CYP24A1 ($P=4.2 \times 10^{-53}$), a gene that encodes the primary catabolic enzyme for 1,25-dihydroxyvitamin D and 25-dihydroxyvitamin D. Each additional copy of the minor allele at this SNP associated with 7% higher serum PTH concentration. The other SNPs associated with serum PTH concentration included rs4074995 within RGS14 ($P=6.6 \times 10^{-17}$), rs219779 adjacent to CLDN14 ($P=3.5 \times 10^{-16}$), rs4443100 near RTDR1 ($P=8.7 \times 10^{-9}$), and rs73186030 near CASR ($P=4.8 \times 10^{-8}$). Of these five SNPs, rs6127099, rs4074995, and rs219779 replicated. Thus, common genetic variants located near genes involved in vitamin D metabolism and calcium and renal phosphate transport associated with differences in circulating PTH concentrations. Future studies could identify the causal variants at these loci, and the clinical and functional relevance of these variants should be pursued.

Rømer Thomsen, K., Callesen, M. B., & Feldstein Ewing, S. W. (2017). **Recommendation to reconsider examining cannabis subtypes together due to opposing effects on brain, cognition and behavior.** *Neuroscience and Biobehavioral Reviews*, 80, 156-158. doi:10.1016/j.neubiorev.2017.05.025

Cannabis use represents a major public health issue throughout the globe. Yet, we still lack the most fundamental knowledge on long-term effects of cannabis on neural, cognitive, and behavioral function. Part of this stems from how cannabis has been measured historically. To this end, most empirical examinations of cannabis have consolidated all types of cannabis collectively. However, this approach obscures differences in how cannabinoids operate. In this commentary, we address the contrasting properties of tetrahydrocannabinol (THC) and cannabidiol (CBD) and their opposing effects on cognitive function. In addition, we address the increase in cannabis potency throughout the past two decades and how that impacts generalizability of early data to evaluations of contemporary public health. We underscore the urgent need for future research to disaggregate examination of THC from CBD, along with the importance of measuring cannabis potency to more effectively unravel its influence on cognitive function and other health issues. © 2017 Elsevier Ltd

Rosenberg, H. F., Fryer, A. D., Munitz, A., Bochner, B. S., Jacoby, D. B., Levi-Schaffer, F., . . . Foster, P. S. (2017). **In Memory and Celebration: Dr. James J. Lee.** *Clinical and Experimental Allergy*. doi:10.1111/cea.12959

We come together to mourn the untimely passing of Dr. James (Jamie) J. Lee, Professor of Biochemistry and Molecular Biology in the Division of Pulmonary Medicine at Mayo Clinic Arizona. A leading scientist, talented teacher, prominent role model, and Eosino-philosopher-in-Chief, Jamie's many enthusiasms and joy for science inspired us all. Together with his wife and research partner, Dr. Nancy Lee, Jamie's academic career was dedicated to improving our understanding of eosinophils and to exploring their contributions to chronic respiratory diseases and cancer. This article is protected by copyright. All rights reserved.

Sakata, K. K., Stephenson, L. S., Mulanax, A., Bierman, J., McGrath, K., Scholl, G., . . . Gold, J. A. (2016). **Professional and interprofessional differences in electronic health records use and recognition of safety issues in critically ill patients.** *J Interprof Care*, 30(5), 636-642. doi:10.1080/13561820.2016.1193479

During interprofessional intensive care unit (ICU) rounds each member of the interprofessional team is responsible for gathering and interpreting information from the electronic health records (EHR) to facilitate effective team decision-making. This study was conducted to determine how each professional group reviews EHR data in preparation for rounds and their ability to identify patient safety issues. Twenty-five physicians, 29 nurses, and 20 pharmacists participated. Individual participants were given verbal and written sign-out and then asked to review a simulated record in our institution's EHR, which contained 14 patient safety items. After reviewing the chart, subjects presented the patient and the number of safety items recognised was recorded. About 40%, 30%, and 26% of safety issues were recognised by physicians, nurses, and pharmacists,

respectively ($p = 0.0006$) and no item recognised 100% of the time. There was little overlap between the three groups with only 50% of items predicted to be recognised 100% of the time by the team. Differential recognition was associated with marked differences in EHR use, with only 3/152 EHR screens utilised by all three groups and the majority of screens used exclusively only by one group. There were significant and non-overlapping differences in individual profession recognition of patient safety issues in the EHR. Preferential identification of safety issues by certain professional groups may be attributed to differences in EHR use. Future studies will be needed to determine if shared decision-making during rounds can improve recognition of safety issues.

Sasaki, T., Rivera-Mulia, J. C., Vera, D., Zimmerman, J., Das, S., Padget, M., . . . Gilbert, D. M. (2017). **Stability of patient-specific features of altered DNA replication timing in xenografts of primary human acute lymphoblastic leukemia.** *Experimental Hematology*, 51, 71-82.e73. doi:10.1016/j.exphem.2017.04.004

Genome-wide DNA replication timing (RT) profiles reflect the global three-dimensional chromosome architecture of cells. They also provide a comprehensive and unique megabase-scale picture of cellular epigenetic state. Thus, normal differentiation involves reproducible changes in RT, and transformation generally perturbs these, although the potential effects of altered RT on the properties of transformed cells remain largely unknown. A major challenge to interrogating these issues in human acute lymphoid leukemia (ALL) is the low proliferative activity of most of the cells, which may be further reduced in cryopreserved samples and difficult to overcome in vitro. In contrast, the ability of many human ALL cell populations to expand when transplanted into highly immunodeficient mice is well documented. To examine the stability of DNA RT profiles of serially passaged xenografts of primary human B- and T-ALL cells, we first devised a method that circumvents the need for bromodeoxyuridine incorporation to distinguish early versus late S-phase cells. Using this and more standard protocols, we found consistently strong retention in xenografts of the original patient-specific RT features. Moreover, in a case in which genomic analyses indicated changing subclonal dynamics in serial passages, the RT profiles tracked concordantly. These results indicate that DNA RT is a relatively stable feature of human ALLs propagated in immunodeficient mice. In addition, they suggest the power of this approach for future interrogation of the origin and consequences of altered DNA RT in ALL. © 2017 ISEH - International Society for Experimental Hematology

Scheer, J. K., Sethi, R. K., Hey, L. A., Lagrone, M. O., Keefe, M., Aryan, H. E., . . . Ames, C. P. (2017). **Results of the 2015 Scoliosis Research Society Survey on Single Versus Dual Attending Surgeon Approach for Adult Spinal Deformity Surgery.** *Spine*, 42(12), 932-942. doi:10.1097/BRS.0000000000002070

Study Design. An electronic survey administered to Scoliosis Research Society (SRS) membership. Objective. To characterize surgeon practices and views regarding the use of two attending surgeons for adult spinal deformity (ASD) surgery. Summary of Background Data. The use of two experienced attending surgeons can decrease the operative time, estimated blood loss, and perioperative complication rates. However, the current practice patterns for the use of two attending surgeons remains unknown. Methods. An electronic, 27-question survey regarding single/dual attending surgeons was administered to the SRS membership. Determinants included: surgeon/practice demographics, assistant type/level of training, and questions regarding use of two attending surgeons. Overall reporting and comparisons between groups were made: US versus international, academic versus private practice, and experience <15 years versus >15 years. Results. A total of 199 surgeons responded from 27 different countries. Overall and between the groups, the respondents significantly reported believing that two attending spine surgeons improves safety, decreases complications, and improves outcomes ($P < 0.01$). Approximately, 67.3% reported using a second attending $\leq 25\%$ of the time (33.2% do not), and 24.1% use one $\geq 51\%$ of the time (similar between groups); 51.1% that have a second attending feel it's limited by reimbursement and access concerns and 71.9% have difficulty getting the second attending reimbursed. 72.3% use a second attending for ALL of the following reasons (no difference between groups): "it's safer/reduces complications," "it decreases operative time," "it decreases blood loss," "it results in improved outcomes," "it's less work and stress for me." If reimbursement was equal/assured for a second attending, 67.5% would use one "more often" or "always." Conclusion. The

respondents feel that having a second attending surgeon improves patient care, however most do not use one often. Reasons include reimbursement/access concerns and the majority would use one if reimbursement was equal and assured. Based on the current literature and these results, there is a need for working with third party payers to improve dual surgeon reimbursement rates in complex cases. © 2017 Wolters Kluwer Health, Inc. All rights reserved.

Scheuer, H., Alarcón, G., Demeter, D. V., Earl, E., Fair, D. A., & Nagel, B. J. (2017). **Reduced fronto-amygdalar connectivity in adolescence is associated with increased depression symptoms over time.** *Psychiatry Research - Neuroimaging*, 266, 35-41. doi:10.1016/j.psychres.2017.05.012

Depression is common among adolescents, affecting greater than 12% of youth in a given year. Studies have shown aberrant amygdala connectivity in depressed adolescents, compared with controls; however, no studies have examined whether these abnormalities precede and heighten risk for depressive symptom expression. This study used resting state functional connectivity (RSFC) magnetic resonance imaging to examine neurobiological markers of escalating depression symptoms in adolescents (ages 12–16 years; free from psychopathology at baseline). Of a large sample of adolescents, 18 showed ≥ 1 S.D. increase in depression scale t-scores over time ("escalators" time to escalation ranging from 6 to 54 months in follow up) and were matched and compared to 19 youth showing stable CDI scores over time ("controls"). Whole-brain analyses on baseline RSFC data using an amygdala seed region-of-interest (ROI) showed that controls had greater RSFC, relative to escalators, between the right amygdala and left inferior frontal and supramarginal gyrus and right mid-cingulate cortex. Additionally, relative to escalators, control youth had less RSFC between the left amygdala and cerebellum. Findings suggest a possible neurobiological marker of increasing depressive symptoms during adolescence, characterized in part by reduced fronto-limbic connectivity, suggesting a premorbid deficiency in top-down emotional regulation. © 2017 Elsevier Ireland Ltd

Schmid, H. A., Brue, T., Colao, A., Gadelha, M. R., Shimon, I., Kapur, K., . . . Fleseriu, M. (2016). **Effect of pasireotide on glucose- and growth hormone-related biomarkers in patients with inadequately controlled acromegaly.** *Endocrine*, 53(1), 210-219. doi:10.1007/s12020-016-0895-8

The purpose of this study was to gain more insight into the mechanism of action of pasireotide in patients who completed the PAOLA study. PAOLA was a 24-week, Phase III, randomized, three-arm study of pasireotide LAR 40 and 60 mg versus octreotide LAR 30 mg or lanreotide Autogel 120 mg in patients with inadequately controlled acromegaly. The current work was a planned exploratory objective of the PAOLA study that evaluated changes in levels of growth hormone (GH), insulin-like growth factor 1 (IGF-1), IGF-binding proteins (IGFBP-2, IGFBP-3), glycated haemoglobin (HbA1c) and fasting plasma glucose (FPG) in each treatment arm. Responders to pasireotide LAR (mean GH levels < 2.5 $\mu\text{g/L}$ and normal IGF-1 levels at 24 weeks) had lower GH and IGF-1 levels at baseline (GH 5.1 ng/mL, IGF-1 519 ng/mL) than non-responders (GH 7.9 ng/mL, IGF-1 672 ng/mL). Frequency of hyperglycaemia after pasireotide treatment was similar in responders and non-responders and depended more on the baseline FPG level. 47 % of all patients treated with pasireotide LAR (40 or 60 mg) did not receive antidiabetic medication at any time during this study. This is the first study to evaluate the treatment effect of pasireotide on key hormonal and glycaemic biomarkers and to identify potential predictors of pasireotide-associated hyperglycaemia. Pre-treatment glucose status may be predictive of the development of pasireotide-associated hyperglycaemia. A large subset of patients with acromegaly does not experience major disturbances in glucose homeostasis while receiving pasireotide LAR.

Sdrulla, A., & Chen, G. (2016). **Minimally invasive procedures for neuropathic pain.** *Pain management*, 6(2), 103-109. doi:10.2217/pmt.15.61

Neuropathic pain is "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system". The prevalence of neuropathic pain ranges from 7 to 11% of the population and minimally invasive

procedures have been used to both diagnose and treat neuropathic pain. Diagnostic procedures consist of nerve blocks aimed to isolate the peripheral nerve implicated, whereas therapeutic interventions either modify or destroy nerve function. Procedures that modify how nerves function include epidural steroid injections, peripheral nerve blocks and sympathetic nerve blocks. Neuroablative procedures include radiofrequency ablation, cryoanalgesia and neurectomies. Currently, neuromodulation with peripheral nerve stimulators and spinal cord stimulators are the most evidence-based treatments of neuropathic pain.

Seifert, H. A., Benedek, G., Liang, J., Nguyen, H., Kent, G., Vandenbark, A. A., . . . Offner, H. (2017). **Sex differences in regulatory cells in experimental stroke.** *Cellular Immunology*. doi:10.1016/j.cellimm.2017.06.003

Stroke is the leading cause of disability in the United States. Sex differences, including smaller infarcts in females and greater involvement of immune-mediated inflammation in males may affect the efficacy of immune-modulating interventions. To address these differences, we sought to identify distinct stroke-modifying mechanisms in female vs. male mice. The current study demonstrated smaller infarcts and increased levels of regulatory CD19+CD5+CD1dhi B10 cells as well as anti-inflammatory CD11b+CD206+ microglia/macrophages in the ipsilateral vs. contralateral hemisphere of female but not male mice undergoing 60min middle cerebral artery occlusion followed by 96h of reperfusion. Moreover, female mice with MCAO had increased total spleen cell numbers but lower B10 levels in spleens. These results elucidate differing sex-dependent regulatory mechanisms that account for diminished stroke severity in females and underscore the need to test immune-modulating therapies for stroke in both males and females. © 2017 Elsevier Inc.

Sheets, L., He, X. J., Olt, J., Schreck, M., Petralia, R. S., Wang, Y. X., . . . Kindt, K. S. (2017). **Enlargement of Ribbons in Zebrafish Hair Cells Increases Calcium Currents But Disrupts Afferent Spontaneous Activity and Timing of Stimulus Onset.** *J Neurosci*, 37(26), 6299-6313. doi:10.1523/jneurosci.2878-16.2017

In sensory hair cells of auditory and vestibular organs, the ribbon synapse is required for the precise encoding of a wide range of complex stimuli. Hair cells have a unique presynaptic structure, the synaptic ribbon, which organizes both synaptic vesicles and calcium channels at the active zone. Previous work has shown that hair-cell ribbon size is correlated with differences in postsynaptic activity. However, additional variability in postsynapse size presents a challenge to determining the specific role of ribbon size in sensory encoding. To selectively assess the impact of ribbon size on synapse function, we examined hair cells in transgenic zebrafish that have enlarged ribbons, without postsynaptic alterations. Morphologically, we found that enlarged ribbons had more associated vesicles and reduced presynaptic calcium-channel clustering. Functionally, hair cells with enlarged ribbons had larger global and ribbon-localized calcium currents. Afferent neuron recordings revealed that hair cells with enlarged ribbons resulted in reduced spontaneous spike rates. Additionally, despite larger presynaptic calcium signals, we observed fewer evoked spikes with longer latencies from stimulus onset. Together, our work indicates that hair-cell ribbon size influences the spontaneous spiking and the precise encoding of stimulus onset in afferent neurons. SIGNIFICANCE STATEMENT Numerous studies support that hair-cell ribbon size corresponds with functional sensitivity differences in afferent neurons and, in the case of inner hair cells of the cochlea, vulnerability to damage from noise trauma. Yet it is unclear whether ribbon size directly influences sensory encoding. Our study reveals that ribbon enlargement results in increased ribbon-localized calcium signals, yet reduces afferent spontaneous activity and disrupts the timing of stimulus onset, a distinct aspect of auditory and vestibular encoding. These observations suggest that varying ribbon size alone can influence sensory encoding, and give further insight into how hair cells transduce signals that cover a wide dynamic range of stimuli.

Sheth, K. N., Elm, J. J., Molyneaux, B. J., Hinson, H., Beslow, L. A., Sze, G. K., . . . Kimberly, W. T. (2016). **Safety and efficacy of intravenous glyburide on brain swelling after large hemispheric infarction (GAMES-RP): a randomised, double-blind, placebo-controlled phase 2 trial.** *Lancet Neurol*, 15(11), 1160-1169. doi:10.1016/s1474-4422(16)30196-x

BACKGROUND: Preclinical models of stroke have shown that intravenous glyburide reduces brain swelling and improves survival. We assessed whether intravenous glyburide (RP-1127; glibenclamide) would safely reduce brain swelling, decrease the need for decompressive craniectomy, and improve clinical outcomes in patients presenting with a large hemispheric infarction. **METHODS:** For this double-blind, randomised, placebo-controlled phase 2 trial, we enrolled patients (aged 18-80 years) with a clinical diagnosis of large anterior circulation hemispheric infarction for less than 10 h and baseline diffusion-weighted MRI image lesion volume of 82-300 cm³ on MRI at 18 hospitals in the USA. We used web-based randomisation (1:1) to allocate patients to the placebo or intravenous glyburide group. Intravenous glyburide was given as a 0.13 mg bolus intravenous injection for the first 2 min, followed by an infusion of 0.16 mg/h for the first 6 h and then 0.11 mg/h for the remaining 66 h. The primary efficacy outcome was the proportion of patients who achieved a modified Rankin Scale (mRS) score of 0-4 at 90 days without undergoing decompressive craniectomy. Analysis was by per protocol. Safety analysis included all randomly assigned patients who received the study drug. This trial is registered with ClinicalTrials.gov, number NCT01794182. **FINDINGS:** Between May 3, 2013, and April 30, 2015, 86 patients were randomly assigned but enrolment was stopped because of funding reasons. The funder, principal investigators, site investigators, patients, imaging core, and outcomes personnel were masked to treatment. The per-protocol study population was 41 participants who received intravenous glyburide and 36 participants who received placebo. 17 (41%) patients in the intravenous glyburide group and 14 (39%) in the placebo group had an mRS score of 0-4 at 90 days without decompressive craniectomy (adjusted odds ratio 0.87, 95% CI 0.32-2.32; p=0.77). Ten (23%) of 44 participants in the intravenous glyburide group and ten (26%) of 39 participants in the placebo group had cardiac events (p=0.76), and four of 20 had serious adverse events (two in the intravenous glyburide group and two in the placebo group, p=1.00). One cardiac death occurred in each group (p=1.00). **INTERPRETATION:** Intravenous glyburide was well tolerated in patients with large hemispheric stroke at risk for cerebral oedema. There was no difference in the composite primary outcome. Further study is warranted to assess the potential clinical benefit of a reduction in swelling by intravenous glyburide. **FUNDING:** Remedy Pharmaceuticals.

Shi, Z., Madden, C. J., & Brooks, V. L. (2017). **Arcuate neuropeptide Y inhibits sympathetic nerve activity via multiple neuropathways.** *Journal of Clinical Investigation*. doi:10.1172/jci92008

Obesity increases sympathetic nerve activity (SNA) via activation of proopiomelanocortin neurons in the arcuate nucleus (ArcN), and this action requires simultaneous withdrawal of tonic neuropeptide Y (NPY) sympathoinhibition. However, the sites and neurocircuitry by which NPY decreases SNA are unclear. Here, using designer receptors exclusively activated by designer drugs (DREADDs) to selectively activate or inhibit ArcN NPY neurons expressing agouti-related peptide (AgRP) in mice, we have demonstrated that this neuronal population tonically suppresses splanchnic SNA (SSNA), arterial pressure, and heart rate via projections to the paraventricular nucleus (PVN) and dorsomedial hypothalamus (DMH). First, we found that ArcN NPY/AgRP fibers closely appose PVN and DMH presympathetic neurons. Second, nanoinjections of NPY or an NPY receptor Y1 (NPY1R) antagonist into PVN or DMH decreased or increased SSNA, respectively. Third, blockade of DMH NPY1R reversed the sympathoinhibition elicited by selective, DREADD-mediated activation of ArcN NPY/AgRP neurons. Finally, stimulation of ArcN NPY/AgRP terminal fields in the PVN and DMH decreased SSNA. Considering that chronic obesity decreases ArcN NPY content, we propose that the ArcN NPY neuropathway to the PVN and DMH is pivotal in obesity-induced elevations in SNA.

Sidonio, R. F., Haley, K. M., & Fallaize, D. (2017). **Impact of diagnosis of von Willebrand disease on patient outcomes: Analysis of medical insurance claims data.** *Haemophilia*. doi:10.1111/hae.13292

The inherited bleeding disorder von Willebrand disease (VWD) is challenging to diagnose owing to disease heterogeneity, lack of a definitive laboratory test and variations in diagnostic criteria. We evaluated the impact of diagnosis and diagnostic delay on patient outcomes. The PharMetrics Plus Database was interrogated for medical claims for VWD (ICD-9 286.4) and bleeding events between 1 January 2006 and 30

June 2015. Longitudinal analysis was performed of patients newly diagnosed with VWD (≥ 9 months' continuous enrolment before first VWD claim) through 24 months following diagnosis. In total, 32 028 diagnosed, including 18 182 newly diagnosed, patients were identified. Most patients (72%) were female. Prediagnosis, bleeding symptoms were most commonly managed by a hospitalist/emergency room physician. Misrecognition of VWD was common, with 25% of patients visiting the same specialist type at least twice for an episodic bleed before diagnosis. Thirty-seven percentage of patients had no diagnostic laboratory test within 24 months of their initial diagnostic claim. Bleed claims reduced following diagnosis: 41% and 26% of female and male patients, respectively, had claims in the year prediagnosis, falling to 21% and 9% of patients at 1-2 years postdiagnosis. The proportion of patients with multiple bleed claims also decreased, from 17% to 6% (females) and 7% to 3% (males). Serially misrecognized patients continued to have more bleeding episodes than other patients, although bleed frequency was lower than before diagnosis. There is a need for improved patient management from bleeding presentation onward to reduce the time to VWD diagnosis and to enhance patient outcomes.

Soni, S., Abdel-Azim, H., McManus, M., Nemecek, E., Sposto, R., Woolfrey, A., & Frangoul, H. (2017). **Phase I Study of Clofarabine and 2-Gy Total Body Irradiation as a Nonmyeloablative Preparative Regimen for Hematopoietic Stem Cell Transplantation in Pediatric Patients with Hematologic Malignancies: A Therapeutic Advances in Childhood Leukemia Consortium Study.** *Biology of Blood and Marrow Transplantation*, 23(7), 1134-1141. doi:10.1016/j.bbmt.2017.03.037

Clofarabine is a purine nucleoside analog with immunosuppressive and antileukemic activity and its inclusion in reduced-intensity regimens could potentially improve outcomes. We performed a prospective phase I study of clofarabine combined with 2 Gy total body irradiation (TBI) as a nonmyeloablative preparative regimen for allogeneic stem cell transplantation in pediatric patients who were considered at high risk of mortality from standard myeloablative regimens. The main goal of the study was to delineate the maximum feasible dose (MFD) of clofarabine in combination with 2 Gy TBI. Eighteen patients, 1 to 21 years of age and in complete remission, were enrolled in 2 strata (matched related donor and unrelated donor) and evaluated for day 100 dose-limiting events (DLE) (nonengraftment, nonrelapse mortality [NRM], and severe renal insufficiency) after receiving clofarabine at the starting dose level of 40 mg/m². All 6 patients (3 in each stratum) engrafted with no day 100 DLE seen in the first cohort. The dose was increased to 52 mg/m² in the next and an expanded cohort (total of 12 patients) and no DLE were observed at day 100 and at the 1-year study endpoint. The regimen was well tolerated with transient transaminitis and gastrointestinal and skin reactions as the common reversible toxicities observed with clofarabine. The dose of 52 mg/m² of clofarabine was deemed the MFD. Disease relapse led to mortality in 6 (33%) patients during follow-up with 1-year event-free survival and overall survival of 60% (95% confidence interval [CI], 34 to 79) and 71% (95% CI, 44 to 87), respectively. This regimen leads to successful engraftment using both related and unrelated donors with exceptionally low rates of NRM. © 2017 The American Society for Blood and Marrow Transplantation

Sonnenberg, A. (2017). **When to stop testing.** *American Journal of Gastroenterology*, 112(6), 970-971. doi:10.1038/ajg.2017.89

Sonpavde, G., Pond, G. R., Plets, M., Tangen, C. M., Hussain, M. H. A., Lara, P. N., . . . Quinn, D. I. (2017). **Validation of the Association of RECIST Changes With Survival in Men With Metastatic Castration-Resistant Prostate Cancer Treated on SWOG Study S0421.** *Clinical Genitourinary Cancer*. doi:10.1016/j.clgc.2017.05.014

Background: Phase 2 trials evaluating new agents for metastatic castration-resistant prostate cancer (mCRPC) have relied on bone scan and prostate-specific antigen changes to assess activity. Given the increasing detection of measurable disease, Response Evaluation Criteria in Solid Tumors (RECIST) changes warrant consideration to evaluate activity. We validated the association of RECIST 1.0 changes with survival in men with mCRPC

receiving docetaxel. Patients and Methods: Data for men with measurable disease from the Southwest Oncology Group (SWOG) S0421, a phase 3 trial in men with mCRPC receiving docetaxel and prednisone plus placebo or atrasentan, were used. Cox proportional hazards regression was used to evaluate the association of RECIST 1.0 outcomes within 120 days, ie, unconfirmed partial response (uPR), stable disease, and progressive disease (PD), with overall survival (OS) from day 120, adjusted for prognostic factors. Results: Overall, 326 men were evaluable for landmark analysis, of whom 23 had PD, 230 stable disease, and 73 uPR. OS beyond day 120 was significantly different ($P = .004$) among these subgroups, with median (95% confidence interval) OS of 7.1 (3.5-8.8), 13.4 (11.4-15.6), and 16.3 (10.0-19.6) months for those with PD, stable disease, and uPR, respectively. In a multivariable model, the hazard ratio (95% confidence interval) for patients with PD was 2.47 (1.42-4.29) compared to patients with an uPR ($P = .002$). Conclusion: The association of RECIST 1.0 changes with OS in men with mCRPC receiving docetaxel was validated. Given limitations of bone scan and prostate-specific antigen alterations, improvements in objective RECIST 1.0 changes should be reported in phase 2 trials before launching phase 3 trials. © 2017 Elsevier Inc.

Sparks, T. N., Shaffer, B. L., Page, J., & Caughey, A. B. (2017). **Gastroschisis: mortality risks with each additional week of expectant management.** *American Journal of Obstetrics and Gynecology*, 216(1), 66.e61-66.e67. doi:10.1016/j.ajog.2016.08.036

BACKGROUND: Prior studies have evaluated the overall risk of stillbirth in pregnancies with fetal gastroschisis. However, the gestational age at which mortality is minimized, balancing the risk of stillbirth against neonatal mortality, remains unclear. **OBJECTIVE:** We sought to evaluate the gestational age at which prenatal and postnatal mortality risk is minimized for fetuses with gastroschisis. **STUDY DESIGN:** This was a retrospective cohort study of singleton pregnancies delivered between 24 0/7 and 39 6/7 weeks, using 2005 through 2006 US national linked birth and death certificate data. Among pregnancies with fetal gastroschisis, prospective risk of stillbirth and risk of infant death were determined for each gestational age week. Risk of infant death with delivery was further compared to composite fetal/infant mortality risk with expectant management for 1 additional week. **RESULTS:** Among 2,119,049 pregnancies, 860 cases (0.04%) of gastroschisis were identified. The overall stillbirth rate among gastroschisis cases was 4.8%, and infant death occurred in 8.3%. Prospective risk of stillbirth became more consistently elevated beginning at 35 weeks, rising to 13.9 per 1000 pregnancies (95% confidence interval, 10.8-17.1) at 39 weeks. Risk of infant death concurrently nadired in the third trimester, ranging between 62.4-66.8 per 1000 live births between 32-39 weeks. Comparing mortality with expectant management vs delivery, relative risk was significantly greater with expectant management between 37-39 weeks, reaching 1.90 (95% confidence interval, 1.73-2.08) at 39 weeks with a number needed to deliver of 17.49 (95% confidence interval, 15.34-20.32) to avoid 1 excess death. **CONCLUSION:** Risk of prenatal and postnatal mortality for fetuses with gastroschisis may be minimized with delivery as early as 37 weeks.

Spencer, D. C., Sun, F. T., Brown, S. N., Jobst, B. C., Fountain, N. B., Wong, V. S., . . . Quigg, M. (2016). **Circadian and ultradian patterns of epileptiform discharges differ by seizure-onset location during long-term ambulatory intracranial monitoring.** *Epilepsia*, 57(9), 1495-1502. doi:10.1111/epi.13455

OBJECTIVE: Previous studies reporting circadian patterns of epileptiform activity and seizures are limited by (1) short-term recording in an epilepsy monitoring unit (EMU) with altered antiepileptic drugs (AEDs) and sleep, or (2) subjective seizure diary reports. We studied circadian patterns using long-term ambulatory intracranial recordings captured by the NeuroPace RNS System. **METHODS:** Retrospective study of RNS System trial participants with stable detection parameters over a continuous 84-day period. We analyzed all detections and long device-detected epileptiform events (long episodes) and defined a subset of subjects in whom long episodes represented electrographic seizures (LE-SZ). Spectrum resampling determined the dominant frequency periodicity and cosinor analysis identified significant circadian peaks in detected activity. Chi-square analysis was used to compare subjects grouped by region of seizure onset. **RESULTS:** In the 134 subjects, detections showed a strongly circadian and uniform pattern irrespective of region of onset that peaked during normal sleep hours. In contrast, long episodes and LE-SZ patterns varied by region.

Neocortical regions had a monophasic, nocturnally dominant rhythm, whereas limbic regions showed a more complex pattern and diurnal peak. Rhythms in some individual limbic subjects were best fit by a dual oscillator (circadian + ultradian) model. SIGNIFICANCE: Epileptiform activity has a strong 24 h periodicity with peak nocturnal occurrence. Limbic and neocortical epilepsy show divergent circadian influences. These findings confirm that circadian patterns of epileptiform activity vary by seizure-onset zone, with implications for treatment and safety, including SUDEP.

Spencer, P. S., Schmutzhard, E., & Winkler, A. S. (2017). **Nodding Syndrome in the Spotlight – Placing Recent Findings in Perspective.** *Trends in Parasitology*, 33(7), 490-492. doi:10.1016/j.pt.2017.05.001

Nodding syndrome (NS) is a debated scientific topic. A recently published study suggests that NS is an autoimmune disorder based on findings of cross-reacting antibodies between neuronal structures and a protein present in *Onchocerca volvulus* (OV). In our opinion, the proposed causal relationship between OV infection and NS has yet to be demonstrated and, instead, OV infection in NS may be opportunistic. © 2017 Elsevier Ltd

Steffens, N. M., Tucholka, J. L., Nabozny, M. J., Schmick, A. E., Brasel, K. J., & Schwarze, M. L. (2016). **Engaging Patients, Health Care Professionals, and Community Members to Improve Preoperative Decision Making for Older Adults Facing High-Risk Surgery.** *JAMA Surg*, 151(10), 938-945. doi:10.1001/jamasurg.2016.1308

Importance: Older patients are at greater risk for postoperative complications, yet they are less likely than younger patients to ask questions about surgery. Objective: To design an intervention to improve preoperative decision making and manage postoperative expectations. Design, Setting, and Participants: A Patient and Family Advisory Council (PFAC) was created to help identify preoperative decisional needs. The PFAC included 4 men and women who had previous experience with high-risk surgery as older patients or their family members; the PFAC met monthly at a local library from May 2014 to April 2015 to examine findings from a prior qualitative study and to integrate themes with PFAC members' experiences. Patient observations included 91 recorded conversations between patients and surgeons and 61 patient interviews before and after surgery. The PFAC members and other stakeholders evaluated 118 publicly available questions and selected 12 corresponding to identified needs to generate a question prompt list (QPL). Three focus groups, including 31 community members from diverse backgrounds, were conducted at community centers in Madison and Milwaukee, Wisconsin, to refine the QPL. A clinical pilot with 42 patients considering surgery was conducted in one outpatient surgical clinic in Madison. Main Outcomes and Measures: Generation of a QPL to address patients' preoperative informational and decisional needs. Results: Through exploration of qualitative data, the PFAC noted 3 critical problems. Patients and family members believed surgery had to be done, were surprised that postoperative recovery was difficult, and lacked knowledge about the perioperative use of advance directives. The PFAC identified a need for more information and decisional support during preoperative conversations that included clarification of treatment options, setting postoperative expectations, and advance care planning. The following 3 question prompt categories arose: "Should I have surgery?" "What should I expect if everything goes well?" and "What happens if things go wrong?" The final list included 11 questions within these domains, was understandable in English and Spanish, and was acceptable to patients in the clinic. Conclusions and Relevance: Through direct engagement of stakeholders, a QPL was created to address core decisional and informational needs of surgical patients. Future testing will evaluate whether this list can be used to improve patient engagement and reduce postoperative regret and conflict about postoperative treatments.

Stoner, M. C., Calligaro, K. D., Chaer, R. A., Dietzek, A. M., Farber, A., Guzman, R. J., . . . Yamaguchi, D. J. (2016). **Reporting standards of the Society for Vascular Surgery for endovascular treatment of chronic lower extremity peripheral artery disease.** *Journal of Vascular Surgery*, 64(1), e1-e21. doi:10.1016/j.jvs.2016.03.420

Peripheral arterial disease (PAD) represents a spectrum from asymptomatic stenosis to limb-threatening ischemia. The last decade has seen a tremendous increase in the variety of endovascular devices and techniques to treat occlusive disease. Like many evolving technologies, the literature surrounding therapy for endovascular arterial disease consists of mixed-quality manuscripts without clear standardization. Accordingly, critical evaluation of the reported results may be problematic. As such, providers and their patients make treatment decisions without the full benefit of a comparative effectiveness framework. The purpose of this document is to provide a summary for the reporting of endovascular revascularization techniques in the setting of chronic disease. Much of the work in this document is based on prior publications and standards proposed by the Society for Vascular Surgery. We have also made recommendations based on current literature and have attempted to acknowledge shortcomings and areas for future research. The various sections contain summaries of required reporting standards and should serve as a guide for the design of clinical trials and as reference for journal editors and reviewers when considering scientific work pertaining to endovascular therapy for chronic lower extremity arterial disease. An Appendix is provided with commonly used abbreviations in this document.

Strong, A. L., Nauta, A. C., & Kuang, A. A. (2015). **Local Wound Care for Primary Cleft Lip Repair: Treatment and Outcomes With use of Topical Hydrogen Peroxide.** *Wounds, 27*(12), 319-326.

OBJECTIVES: This study highlights and validates a peroxide-based wound healing strategy for treatment of surgically closed facial wounds in a pediatric population. The authors identified pediatric patients undergoing primary cleft lip repair as a specific population to evaluate the outcomes of such a protocol. Through analysis of defined outcome measures, a reliable and reproducible protocol for postoperative wound care following primary cleft lip repair with favorable results is described. **METHODS:** This retrospective study analyzes wound healing outcomes in pediatric patients undergoing primary cleft lip repair from 2006 to 2011 at a tertiary academic center. The wound healing protocol was used in both primary unilateral and bilateral repairs. One hundred fortysix patients between the ages of 0 and 4 years underwent primary cleft lip repair and cleft rhinoplasty by a single, fellowship-trained craniofacial surgeon. Postoperatively, wounds were treated with half-strength hydrogen peroxide and bacitracin, as well as scar massage. Incisional dehiscence, hypertrophic scar formation, discoloration, infection, and reoperation were studied. Outcomes were evaluated in light of parent compliance, demographics, preoperative nasolabial molding (PNAM), and diagnosis. **RESULTS:** The authors identified 146 patients for inclusion in this study. There was no wound or incisional dehiscence. One hundred twenty-four patients demonstrated favorable cosmetic outcome. Only 3 (2%) of patients who developed suboptimal outcomes underwent secondary surgical revision (> 1 year after surgery). Demographic differences were not statistically significant, and PNAM treatment did not influence outcomes. **CONCLUSION:** These data validate the use of half-strength hydrogen peroxide and bacitracin as part of a wound healing strategy in pediatric incisional wounds. The use of hydrogen peroxide produced comparable outcomes to previously published studies utilizing other wound healing strategies and, therefore, these study findings support the further use of this regimen for this particular population.

Sullivan, L. S., Bowne, S. J., Koboldt, D. C., Cadena, E. L., Heckenlively, J. R., Branham, K. E., . . . Daiger, S. P. (2017). **A Novel Dominant Mutation in SAG, the Arrestin-1 Gene, Is a Common Cause of Retinitis Pigmentosa in Hispanic Families in the Southwestern United States.** *Invest Ophthalmol Vis Sci, 58*(5), 2774-2784. doi:10.1167/iops.16-21341

Purpose: To identify the causes of autosomal dominant retinitis pigmentosa (adRP) in a cohort of families without mutations in known adRP genes and consequently to characterize a novel dominant-acting missense mutation in SAG. **Methods:** Patients underwent ophthalmologic testing and were screened for mutations using targeted-capture and whole-exome next-generation sequencing. Confirmation and additional screening were done by Sanger sequencing. Haplotypes segregating with the mutation were determined using short tandem repeat and single nucleotide variant polymorphisms. Genealogies were established by interviews of family members. **Results:** Eight families in a cohort of 300 adRP families, and four additional families, were found to have a novel heterozygous mutation in the SAG gene, c.440G>T; p.Cys147Phe.

Patients exhibited symptoms of retinitis pigmentosa and none showed symptoms characteristic of Oguchi disease. All families are of Hispanic descent and most were ascertained in Texas or California. A single haplotype including the SAG mutation was identified in all families. The mutation dramatically alters a conserved amino acid, is extremely rare in global databases, and was not found in 4000+ exomes from Hispanic controls. Molecular modeling based on the crystal structure of bovine arrestin-1 predicts protein misfolding/instability. Conclusions: This is the first dominant-acting mutation identified in SAG, a founder mutation possibly originating in Mexico several centuries ago. The phenotype is clearly adRP and is distinct from the previously reported phenotypes of recessive null mutations, that is, Oguchi disease and recessive RP. The mutation accounts for 3% of the 300 families in the adRP Cohort and 36% of Hispanic families in this cohort.

Tarhini, A. A., Lorigan, P., & Leachman, S. (2017). **Operable Melanoma: Screening, Prognostication, and Adjuvant and Neoadjuvant Therapy.** *Am Soc Clin Oncol Educ Book*, 37, 651-660. doi:10.14694/edbk_174930

The importance of reducing the numbers of patients with late-stage melanoma, identifying which patients are most likely to progress, and treating these patients at the earliest possible stage cannot be overemphasized. Improved screening of patients prior to diagnosis has the advantage of identifying early-stage disease that is for the most part treatable by surgical methods. The process of melanoma screening is rapidly evolving through population-based programs, mobile health technologies, and advanced imaging tools. For patients with newly diagnosed melanoma, accurately estimating disease prognosis has important implications for management and follow-up. Prognostic factors are individual host- or tumor-related factors or molecules that correlate with genetic predisposition and clinical course. These include clinical covariates and host and tumor proteomic/genomic markers that allow the prognostic subclassification of patients. Adjuvant therapy for high-risk surgically resected melanoma targets residual micrometastatic disease with the goal of reducing the risk of relapse and mortality. In the United States, three regimens have achieved regulatory approval for adjuvant therapy, including high-dose interferon alpha, pegylated interferon alpha, and ipilimumab at 10 mg/kg. Phase III trials have reported benefits in relapse-free survival (all regimens) and overall survival (high-dose interferon alpha and ipilimumab). The management of locally/regionally advanced melanoma may benefit from neoadjuvant therapy, which is the subject of several ongoing studies. Recent studies have shown promising clinical activity and yielded important biomarker findings and mechanistic insights.

Taylor, L. J., Rathouz, P. J., Berlin, A., Brasel, K. J., Mosenthal, A. C., Finlayson, E., . . . Schwarze, M. L. (2017). **Navigating high-risk surgery: protocol for a multisite, stepped wedge, cluster-randomised trial of a question prompt list intervention to empower older adults to ask questions that inform treatment decisions.** *BMJ Open*, 7(5), e014002. doi:10.1136/bmjopen-2016-014002

INTRODUCTION: Older patients frequently undergo operations that carry high risk for postoperative complications and death. Poor preoperative communication between patients and surgeons can lead to uninformed decisions and result in unexpected outcomes, conflict between surgeons and patients, and treatment inconsistent with patient preferences. This article describes the protocol for a multisite, cluster-randomised trial that uses a stepped wedge design to test a patient-driven question prompt list (QPL) intervention aimed to improve preoperative decision making and inform postoperative expectations. **METHODS AND ANALYSIS:** This Patient-Centered Outcomes Research Institute-funded trial will be conducted at five academic medical centres in the USA. Study participants include surgeons who routinely perform vascular or oncological surgery, their patients and families. We aim to enrol 40 surgeons and 480 patients over 24 months. Patients age 65 or older who see a study-enrolled surgeon to discuss a vascular or oncological problem that could be treated with high-risk surgery will be enrolled at their clinic visit. Together with stakeholders, we developed a QPL intervention addressing preoperative communication needs of patients considering major surgery. Guided by the theories of self-determination and relational autonomy, this intervention is designed to increase patient activation. Patients will receive the QPL brochure and a letter from their surgeon encouraging its use. Using audio recordings of the outpatient surgical consultation, patient and family member questionnaires administered at three time points and retrospective chart review, we will compare

the effectiveness of the QPL intervention to usual care with respect to the following primary outcomes: patient engagement in decision making, psychological well-being and post-treatment regret for patients and families, and interpersonal and intrapersonal conflict relating to treatment decisions and treatments received. ETHICS AND DISSEMINATION: Approvals have been granted by the Institutional Review Board at the University of Wisconsin and at each participating site, and a Certificate of Confidentiality has been obtained. Results will be reported in peer-reviewed publications and presented at national meetings. TRIAL REGISTRATION NUMBER: NCT02623335.

Tereshchenko, L. G., Kim, E. D., Oehler, A., Meoni, L. A., Ghafoori, E., Rami, T., . . . Parekh, R. S. (2016).

Electrophysiologic Substrate and Risk of Mortality in Incident Hemodialysis. *J Am Soc Nephrol*, 27(11), 3413-3420. doi:10.1681/asn.2015080916

The single leading cause of mortality on hemodialysis is sudden cardiac death. Whether measures of electrophysiologic substrate independently associate with mortality is unknown. We examined measures of electrophysiologic substrate in a prospective cohort of 571 patients on incident hemodialysis enrolled in the Predictors of Arrhythmic and Cardiovascular Risk in End Stage Renal Disease Study. A total of 358 participants completed both baseline 5-minute and 12-lead electrocardiogram recordings on a nondialysis day. Measures of electrophysiologic substrate included ventricular late potentials by the signal-averaged electrocardiogram and spatial mean QRS-T angle measured on the averaged beat recorded within a median of 106 days (interquartile range, 78-151 days) from dialysis initiation. The cohort was 59% men, and 73% were black, with a mean \pm SD age of 55 \pm 13 years. Transthoracic echocardiography revealed a mean \pm SD ejection fraction of 65.5% \pm 12.0% and a mean \pm SD left ventricular mass index of 66.6 \pm 22.3 g/m². During 864.6 person-years of follow-up, 77 patients died; 35 died from cardiovascular causes, of which 15 were sudden cardiac deaths. By Cox regression analysis, QRS-T angle \geq 75 degrees significantly associated with increased risk of cardiovascular mortality (hazard ratio, 2.99; 95% confidence interval, 1.31 to 6.82) and sudden cardiac death (hazard ratio, 4.52; 95% confidence interval, 1.17 to 17.40) after multivariable adjustment for demographic, cardiovascular, and dialysis factors. Abnormal signal-averaged electrocardiogram measures did not associate with mortality. In conclusion, spatial QRS-T angle but not abnormal signal-averaged electrocardiogram significantly associates with cardiovascular mortality and sudden cardiac death independent of traditional risk factors in patients starting hemodialysis.

Tessier, C. D. (2017). **Editorial Commentary.** *Urology Practice*, 4(4), 301. doi:10.1016/j.urpr.2016.08.009

Thomas, C. R., Jr., & Shyr, Y. (2017). **Determining penetration of prostate-specific antigen screening recommendations.** *JAMA Oncology*, 3(5), 707. doi:10.1001/jamaoncol.2016.5978

Thuro, B. A., Sagiv, O., Shinder, R., Debnam, J. M., Ozgur, O., Ng, J. D., . . . Esmaeli, B. (2017). **Clinical Presentation and Anatomical Location of Orbital Plasmacytomas.** *Ophthalmic Plastic and Reconstructive Surgery*. doi:10.1097/IOP.0000000000000939

PURPOSE: To evaluate the clinical and anatomical location of orbital plasmacytomas and assess local control following therapy. **METHODS:** The American Society of Ophthalmic Plastic and Reconstructive Surgery Oncology Database was queried to identify patients diagnosed with orbital plasmacytoma. These patients' records were reviewed for demographic characteristics, clinical and radiologic findings, treatments, and outcomes. **RESULTS:** Thirty patients from 4 institutions (24 from MD Anderson Cancer Center, 3 from SUNY Downstate Medical Center, 2 from University of California, Los Angeles, and 1 from Oregon Health and Science University) were identified. Eighteen patients (60%) were diagnosed with multiple myeloma (MM) before and 11 (37%) were diagnosed with MM immediately after orbital plasmacytoma. Based on imaging, 4

distinct anatomical patterns were identified: 1) bony plasmacytoma affecting the superotemporal orbit, epidural space, and temporal fossa (15 patients; 50%); 2) discrete orbital plasmacytoma (7 patients; 23%); 3) infiltrative plasmacytoma either originating from a sinus (4 patients; 13%); or 4) originating from the orbital floor and infiltrating facial soft tissue (4 patients; 13%). Of the 29 patients with available treatment data, 2 had radiation only, 3 had chemotherapy only, 6 had chemoradiation, and 18 had stem cell transplant following chemoradiation (n = 17) or only chemotherapy (n = 1). Following treatment, 10 patients achieved complete and 11 achieved partial responses. **CONCLUSION:** Orbital plasmacytomas were found exclusively in patients with MM diagnosed before or immediately after orbital plasmacytoma. Plasmacytomas can have 4 distinct anatomical patterns of origin. Following treatment, all patients had good to excellent local control of their orbital lesions. © 2017 by The American Society of Ophthalmic Plastic and Reconstructive Surgery, Inc., All rights reserved.

Tojais, N. F., Cao, A., Lai, Y. J., Wang, L., Chen, P. I., Alcazar, M. A. A., . . . Rabinovitch, M. (2017). **Codependence of Bone Morphogenetic Protein Receptor 2 and Transforming Growth Factor-beta in Elastic Fiber Assembly and Its Perturbation in Pulmonary Arterial Hypertension.** *Arteriosclerosis, Thrombosis, and Vascular Biology*. doi:10.1161/atvbaha.117.309696

OBJECTIVE: We determined in patients with pulmonary arterial (PA) hypertension (PAH) whether in addition to increased production of elastase by PA smooth muscle cells previously reported, PA elastic fibers are susceptible to degradation because of their abnormal assembly. **APPROACH AND RESULTS:** Fibrillin-1 and elastin are the major components of elastic fibers, and fibrillin-1 binds bone morphogenetic proteins (BMPs) and the large latent complex of transforming growth factor-beta1 (TGFbeta1). Thus, we considered whether BMPs like TGFbeta1 contribute to elastic fiber assembly and whether this process is perturbed in PAH particularly when the BMP receptor, BMPR2, is mutant. We also assessed whether in mice with *Bmpr2/1a* compound heterozygosity, elastic fibers are susceptible to degradation. In PA smooth muscle cell and adventitial fibroblasts, TGFbeta1 increased elastin mRNA, but the elevation in elastin protein was dependent on BMPR2; TGFbeta1 and BMP4, via BMPR2, increased extracellular accumulation of fibrillin-1. Both BMP4- and TGFbeta1-stimulated elastic fiber assemblies were impaired in idiopathic (I) PAH-PA adventitial fibroblast versus control cells, particularly those with hereditary (H) PAH and a BMPR2 mutation. This was related to profound reductions in elastin and fibrillin-1 mRNA. Elastin protein was increased in IPAH PA adventitial fibroblast by TGFbeta1 but only minimally so in BMPR2 mutant cells. Fibrillin-1 protein increased only modestly in IPAH or HPAH PA adventitial fibroblast stimulated with BMP4 or TGFbeta1. In *Bmpr2/1a* heterozygote mice, reduced PA fibrillin-1 was associated with elastic fiber susceptibility to degradation and more severe pulmonary hypertension. **CONCLUSIONS:** Disrupting BMPR2 impairs TGFbeta1- and BMP4-mediated elastic fiber assembly and is of pathophysiologic significance in PAH.

Tolcos, M., Petratos, S., Hirst, J. J., Wong, F., Spencer, S. J., Azhan, A., . . . Walker, D. W. (2017). **Blocked, delayed, or obstructed: What causes poor white matter development in intrauterine growth restricted infants?** *Progress in Neurobiology*, 154, 62-77. doi:10.1016/j.pneurobio.2017.03.009

Poor white matter development in intrauterine growth restricted (IUGR) babies remains a major, untreated problem in neonatology. New therapies, guided by an understanding of the mechanisms that underlie normal and abnormal oligodendrocyte development and myelin formation, are required. Much of our knowledge of the mechanisms that underlie impaired myelination come from studies in adult demyelinating disease, preterm brain injury, or experimental models of hypoxia-ischemia. However, relatively less is known for IUGR which is surprising because IUGR is a leading cause of perinatal mortality and morbidity, second only to premature birth. IUGR is also a significant risk factor for the later development of cerebral palsy, and is a greater risk compared to some of the more traditionally researched antecedents – asphyxia and inflammation. Recent evidence suggests that the white matter injury and reduced myelination in the brains of some preterm babies is due to impaired maturation of oligodendrocytes thereby resulting in the reduced capacity to synthesize myelin. Therefore, it is not surprising that the hypomyelination observable in the central nervous system of IUGR infants has similarly lead to investigations identifying a delay or blockade in the progress of

maturation of oligodendrocytes in these infants. This review will discuss current ideas thought to account for the poor myelination often present in the neonate's brain following IUGR, and discuss novel interventions that are promising as treatments that promote oligodendrocyte maturation, and thereby repair the myelination deficits that otherwise persist into infancy and childhood and lead to neurodevelopmental abnormalities. © 2017 Elsevier Ltd

Tolle, S. W., & Teno, J. M. (2017). **Lessons from End-of-Life Care in Oregon.** *N Engl J Med*, 376(21), 2096. doi:10.1056/NEJMc1704727

Townend, J., Minelli, C., Mortimer, K., Obaseki, D. O., Al Ghobain, M., Cherkaski, H., . . . Burney, P. G. J. (2017). **The association between chronic airflow obstruction and poverty in 12 sites of the multinational BOLD study.** *European Respiratory Journal*, 49(6). doi:10.1183/13993003.01880-2016

Poverty is strongly associated with mortality from COPD, but little is known of its relation to airflow obstruction. In a cross-sectional study of adults aged ≥ 40 years from 12 sites (N=9255), participating in the Burden of Obstructive Lung Disease (BOLD) study, poverty was evaluated using a wealth score (0-10) based on household assets. Obstruction, measured as forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) (%) after administration of 200 μ g salbutamol, and prevalence of FEV1/FVC < lower limit of normal were tested for association with poverty for each site, and the results were combined by meta-analysis. Mean wealth scores ranged from 4 in Blantyre (Malawi) and Kashmir (India) to 10 in Riyadh (Saudi Arabia), and the prevalence of obstruction, from 16% in Kashmir to 3% in Riyadh and Penang (Malaysia). Following adjustments for age and sex, FEV1/FVC increased by 0.36% (absolute change) (95%CI: 0.22, 0.49; $p < 0.001$) per unit increase in wealth score. Adjustments for other confounders reduced this effect to 0.23% (0.11, 0.34), but even this value remained highly significant ($p < 0.001$). Results were consistent across sites ($I^2 = 1\%$; $\text{phet} = 0.44$). Mean wealth scores explained 38% of the variation in mean FEV1/FVC between sites ($r^2 = 0.385$, $p = 0.031$). Airflow obstruction is consistently associated with poverty at individual and community levels across several countries. Copyright © ERS 2017.

True, C., Takahashi, D., Kirigiti, M., Lindsley, S. R., Moctezuma, C., Arik, A., . . . Grove, K. L. (2017). **Arcuate nucleus neuropeptide coexpression and connections to gonadotrophin-releasing hormone neurones in the female rhesus macaque.** *Journal of Neuroendocrinology*, 29(6). doi:10.1111/jne.12491

The underlying hypothalamic neurocircuitry by which metabolism and feeding regulates reproductive function has been well-studied in the rodent; however, recent data have demonstrated significant neuroanatomical differences in the human brain. The present study had three objectives, centred on arcuate nucleus neuropeptides regulating feeding and reproduction: (i) to characterise coexpression patterns in the female nonhuman primate; (ii) to establish whether these neuronal populations make potential contacts with gonadotrophin-releasing hormone (GnRH) neurones; and (iii) to determine whether these contacts differ between the low and high GnRH-releasing states of pre-puberty and adulthood, respectively. Female nonhuman primates have several coexpression patterns of hypothalamic neuropeptides that differ from those reported in rodents. Cocaine- and amphetamine-regulated transcript (CART) is not coexpressed with pro-opiomelanocortin but instead with neuropeptide Y (NPY). CART is also expressed in a subpopulation of kisspeptin cells in the nonhuman primate, similar to observations in humans but diverging from findings in rodents. Very few GnRH-expressing neurones received close appositions from double-labelled kisspeptin/CART fibres; however, both single-labelled kisspeptin and CART fibres were in frequent apposition with GnRH neurones, with no differences between prepubertal and adult animals. NPY/agouti-related peptide (AgRP) coexpressing fibres contacted significantly more GnRH neurones in prepubertal animals than adults, consistent with increased NPY and AgRP mRNA observed in prepubertal animals. The findings of the present study detail significant differences in arcuate nucleus neuropeptide coexpression in the monkey

compared to the rodent and are consistent with the hypothesis that arcuate nucleus NPY/AgRP neurones play an inhibitory role in controlling GnRH neuronal regulation in the prepubertal primate.

Tupone, D., Cano, G., & Morrison, S. F. (2017). **Thermoregulatory inversion: A novel thermoregulatory paradigm.** *American Journal of Physiology - Regulatory Integrative and Comparative Physiology*, 312(5), R779-R786. doi:10.1152/ajpregu.00022.2017

To maintain core body temperature in mammals, the normal central nervous system (CNS) thermoregulatory reflex networks produce an increase in brown adipose tissue (BAT) thermogenesis in response to skin cooling and an inhibition of the sympathetic outflow to BAT during skin rewarming. In contrast, these normal thermoregulatory reflexes appear to be inverted in hibernation/torpor; thermogenesis is inhibited during exposure to a cold environment, allowing dramatic reductions in core temperature and metabolism, and thermogenesis is activated during skin rewarming, contributing to a return of normal body temperature. Here, we describe two unrelated experimental paradigms in which rats, a nonhibernating/torpid species, exhibit a "thermoregulatory inversion," which is characterized by an inhibition of BAT thermogenesis in response to skin cooling, and a switch in the gain of the skin cooling reflex transfer function from negative to positive values. Either transection of the neuraxis immediately rostral to the dorsomedial hypothalamus in anesthetized rats or activation of A1 adenosine receptors within the CNS of free-behaving rats produces a state of thermoregulatory inversion in which skin cooling inhibits BAT thermogenesis, leading to hypothermia, and skin warming activates BAT, supporting an increase in core temperature. These results reflect the existence of a novel neural circuit that mediates inverted thermoregulatory reflexes and suggests a pharmacological mechanism through which a deeply hypothermic state can be achieved in nonhibernating/ torpid mammals, possibly including humans. © 2017 the American Physiological Society.

Tyner, J. W. (2017). **Kinase Inhibitor Screening in Myeloid Malignancies.** *Hematology/Oncology Clinics of North America*. doi:10.1016/j.hoc.2017.04.004

Kinase pathways are primary effectors of many targeted therapy approaches for cancer. Kinase pathways can be dysregulated by mechanisms far more diverse than chromosomal rearrangements or point mutations, which drove the initial application of kinase inhibitors to cancer. Functional screening with kinase inhibitors is one tool by which we can understand the diversity of target kinases and candidate drugs for patients before fully understanding the mechanistic rationale for kinase pathway dysregulation. By combining functional screening with genomic data, it is also possible to accelerate understanding of these mechanistic underpinnings. © 2017 Elsevier Inc.

Uhrlaub, J. L., Pulko, V., DeFilippis, V. R., Broeckel, R., Streblow, D. N., Coleman, G. D., . . . Nikolich-Zugich, J. (2016). **Dysregulated TGF-beta Production Underlies the Age-Related Vulnerability to Chikungunya Virus.** *PLoS Pathogens*, 12(10), e1005891. doi:10.1371/journal.ppat.1005891

Chikungunya virus (CHIKV) is a re-emerging global pathogen with pandemic potential, which causes fever, rash and debilitating arthralgia. Older adults over 65 years are particularly susceptible to severe and chronic CHIKV disease (CHIKVD), accounting for >90% of all CHIKV-related deaths. There are currently no approved vaccines or antiviral treatments available to limit chronic CHIKVD. Here we show that in old mice excessive, dysregulated TGFbeta production during acute infection leads to a reduced immune response and subsequent chronic disease. Humans suffering from CHIKV infection also exhibited high TGFbeta levels and a pronounced age-related defect in neutralizing anti-CHIKV antibody production. In vivo reduction of TGFbeta levels minimized acute joint swelling, restored neutralizing antibody production and diminished chronic joint pathology in old mice. This study identifies increased and dysregulated TGFbeta secretion as one key mechanism contributing to the age-related loss of protective anti-CHIKV-immunity leading to chronic CHIKVD.

Urbanski, H. F., Mueller, K., & Bethea, C. (2017). **Effect of an obesogenic diet on circadian activity and serum hormones in old monkeys.** *Endocr Connect.* doi:10.1530/ec-17-0108

Like women, old female rhesus macaques undergo menopause and show many of the same age-associated changes, including perturbed activity/rest cycles and altered circulating levels of many hormones. Previous studies showed that administration of an estrogen agonist increased activity in female monkeys, that hormone therapy (HT) increased activity in postmenopausal women, and that obesity decreased activity in women. The present study sought to determine if postmenopausal activity and circulating hormone levels also respond to HT when monkeys are fed a high-fat, high-sugar Western-style diet (WSD). Old female rhesus macaques were ovariectomized (OvH) to induce surgical menopause, and fed a WSD for 2 years. Half of the animals received estradiol-17beta (E), beginning immediately after OvH, while the other half received placebo. Animals in both groups showed an increase in body weight and a decrease in overall activity levels. These changes were associated with a rise in both day-time and nocturnal serum leptin concentrations, but there was no change in serum concentrations of either cortisol or dehydroepiandrosterone sulfate (DHEAS). These data suggest that 2 years of HT has little or no effect on locomotor activity or circadian hormone patterns in menopausal macaques fed an obesogenic diet.

van der Heijde, D., Deodhar, A., Fleischmann, R., Mease, P. J., Rudwaleit, M., Nurminen, T., & Davies, O. (2017). **Early Disease Activity or Clinical Response as Predictors of Long-Term Outcomes With Certolizumab Pegol in Axial Spondyloarthritis or Psoriatic Arthritis.** *Arthritis Care and Research.* doi:10.1002/acr.23092

Objective: Early identification of patients unlikely to achieve good long-term disease control with anti-tumor necrosis factor therapy in axial spondyloarthritis (SpA) and psoriatic arthritis (PsA) is important for physicians following treat-to-target recommendations. Here we assess associations between disease activity or clinical response during the first 12 weeks of treatment and attainment of treatment targets at week 48 in axial SpA and PsA patients receiving certolizumab pegol. Methods: The relationship between disease activity or clinical response during the first 12 weeks of treatment and achievement of week-48 targets (for axial SpA: inactive disease based on Ankylosing Spondylitis Disease Activity Score [ASDAS] using the C-reactive protein [CRP] level, or Bath Ankylosing Spondylitis Disease Activity Index <2 with normal CRP level; and for PsA: minimal disease activity) was assessed post hoc using RAPID-axSpA and RAPID-PsA trial data. Results: A clear relationship between disease activity from week 2 to 12 and achievement of week-48 treatment targets was observed in both axial SpA and PsA populations. In axial SpA, week-48 ASDAS inactive disease was achieved by 0% of patients (0 of 21) with ASDAS very high disease activity at week 12, compared to 68% of patients (34 of 50) with week-12 ASDAS inactive disease. For PsA, week-48 minimal disease activity was achieved by 0% of patients (0 of 26) with Disease Activity Score in 28 joints (DAS28) using the CRP level >5.1 at week 12, compared to 73% of patients (57 of 78) with DAS28-CRP <2.6. Similar results were observed regardless of the disease activity measure used. Clinical response at week 12 also predicted week-48 outcomes, though to a lesser extent than disease activity. Conclusion: Using disease activity and the clinical response state during the first 12 weeks of certolizumab pegol treatment, it was possible to identify a subset of axial SpA and PsA patients unlikely to achieve long-term treatment goals. © 2016, The Authors.

Venook, A. P., Niedzwiecki, D., Lenz, H. J., Innocenti, F., Fruth, B., Meyerhardt, J. A., . . . Blanke, C. (2017). **Effect of First-Line Chemotherapy Combined With Cetuximab or Bevacizumab on Overall Survival in Patients With KRAS Wild-Type Advanced or Metastatic Colorectal Cancer: A Randomized Clinical Trial.** *Jama, 317*(23), 2392-2401. doi:10.1001/jama.2017.7105

Importance: Combining biologic monoclonal antibodies with chemotherapeutic cytotoxic drugs provides clinical benefit to patients with advanced or metastatic colorectal cancer, but the optimal choice of the initial biologic therapy in previously untreated patients is unknown. Objective: To determine if the addition of cetuximab vs bevacizumab to the combination of leucovorin, fluorouracil, and oxaliplatin (mFOLFOX6) regimen or the combination of leucovorin, fluorouracil, and irinotecan (FOLFIRI) regimen is superior as first-

line therapy in advanced or metastatic KRAS wild-type (wt) colorectal cancer. Design, Setting, and Participants: Patients (≥ 18 years) enrolled at community and academic centers throughout the National Clinical Trials Network in the United States and Canada (November 2005–March 2012) with previously untreated advanced or metastatic colorectal cancer whose tumors were KRAS wt chose to take either the mFOLFOX6 regimen or the FOLFIRI regimen as chemotherapy and were randomized to receive either cetuximab ($n = 578$) or bevacizumab ($n = 559$). The last date of follow-up was December 15, 2015. Interventions: Cetuximab vs bevacizumab combined with either mFOLFOX6 or FOLFIRI chemotherapy regimen chosen by the treating physician and patient. Main Outcomes and Measures: The primary end point was overall survival. Secondary objectives included progression-free survival and overall response rate, site-reported confirmed or unconfirmed complete or partial response. Results: Among 1137 patients (median age, 59 years; 440 [39%] women), 1074 (94%) of patients met eligibility criteria. As of December 15, 2015, median follow-up for 263 surviving patients was 47.4 months (range, 0–110.7 months), and 82% of patients (938 of 1137) experienced disease progression. The median overall survival was 30.0 months in the cetuximab-chemotherapy group and 29.0 months in the bevacizumab-chemotherapy group with a stratified hazard ratio (HR) of 0.88 (95% CI, 0.77–1.01; $P = .08$). The median progression-free survival was 10.5 months in the cetuximab-chemotherapy group and 10.6 months in the bevacizumab-chemotherapy group with a stratified HR of 0.95 (95% CI, 0.84–1.08; $P = .45$). Response rates were not significantly different, 59.6% vs 55.2% for cetuximab and bevacizumab, respectively (difference, 4.4%, 95% CI, 1.0%–9.0%, $P = .13$). Conclusions and Relevance: Among patients with KRAS wt untreated advanced or metastatic colorectal cancer, there was no significant difference in overall survival between the addition of cetuximab vs bevacizumab to chemotherapy as initial biologic treatment. Trial Registration: clinicaltrials.gov identifier: NCT00265850.

Vesco, K. K., Leo, M. C., Karanja, N., Gillman, M. W., McEvoy, C. T., King, J. C., . . . Stevens, V. J. (2016). **One-year postpartum outcomes following a weight management intervention in pregnant women with obesity.** *Obesity (Silver Spring)*, 24(10), 2042–2049. doi:10.1002/oby.21597

OBJECTIVE: This analysis was focused on 1-year maternal and infant follow-up of a randomized trial that tested a weight management intervention conducted during pregnancy. **METHODS:** One hundred fourteen women with obesity (mean BMI 36.7 kg/m²) were randomly assigned at a mean of 15 weeks gestation to a weight management intervention or usual care control condition. The intervention ended at delivery and resulted in less gestational weight gain and a lower proportion of large-for-gestational-age newborns among intervention compared with control participants. The primary outcome at 12 months postpartum was maternal weight. Secondary outcomes included infant weight-for-age and weight-for-length z-scores. **RESULTS:** At 1 year, mothers in the intervention group weighed 96.3 \pm 18.6 kg and those in the control group 99.7 \pm 19.2 kg. There was no significant difference between groups in change in weight from randomization to 1 year postpartum ($b = -0.47$, 95% CI: -4.03 to 3.08). There was a significant main effect of group for infant weight-for-age z-scores ($b = -0.40$, 95% CI: -0.75 to -0.05) but not infant weight-for-length z-scores ($b = -0.20$, 95% CI: -0.59 to 0.20). **CONCLUSIONS:** A gestational weight management intervention did not influence maternal weight or infant weight-for-length at 1 year postpartum. Future studies may be warranted to determine whether extending prenatal interventions into the postpartum period would be beneficial for maternal and infant outcomes.

Wall, J. D., Schlebusch, S. A., Alberts, S. C., Cox, L. A., Snyder-Mackler, N., Nevenon, K. A., . . . Tung, J. (2016). **Genomewide ancestry and divergence patterns from low-coverage sequencing data reveal a complex history of admixture in wild baboons.** *Molecular Ecology*, 25(14), 3469–3483. doi:10.1111/mec.13684

Naturally occurring admixture has now been documented in every major primate lineage, suggesting its key role in primate evolutionary history. Active primate hybrid zones can provide valuable insight into this process. Here, we investigate the history of admixture in one of the best-studied natural primate hybrid zones, between yellow baboons (*Papio cynocephalus*) and anubis baboons (*Papio anubis*) in the Amboseli ecosystem of Kenya. We generated a new genome assembly for yellow baboon and low-coverage

genomewide resequencing data from yellow baboons, anubis baboons and known hybrids ($n = 44$). Using a novel composite likelihood method for estimating local ancestry from low-coverage data, we found high levels of genetic diversity and genetic differentiation between the parent taxa, and excellent agreement between genome-scale ancestry estimates and a priori pedigree, life history and morphology-based estimates ($r(2) = 0.899$). However, even putatively unadmixed Amboseli yellow individuals carried a substantial proportion of anubis ancestry, presumably due to historical admixture. Further, the distribution of shared vs. fixed differences between a putatively unadmixed Amboseli yellow baboon and an unadmixed anubis baboon, both sequenced at high coverage, is inconsistent with simple isolation-migration or equilibrium migration models. Our findings suggest a complex process of intermittent contact that has occurred multiple times in baboon evolutionary history, despite no obvious fitness costs to hybrids or major geographic or behavioural barriers. In combination with the extensive phenotypic data available for baboon hybrids, our results provide valuable context for understanding the history of admixture in primates, including in our own lineage.

Wang, Y., Wu, S., & Liu, H. (2016). *MayoNLPTeam at the 2016 CLEF eHealth information retrieval task 1*.

This paper presents the participation of MayoNLPTeam in the 2016 CLEF eHealth Information Retrieval Task (IR Task 1: Ad-hoc search). We explored a Part-of-Speech (POS) based query term weighting approach which assigns different weights to the query terms according to their POS categories. The weights are learned by defining an objective function based on the mean average precision. We applied the proposed approach with the optimal weights obtained from TREC 2011 and 2012 Medical Records Track into the Query Likelihood model (Run 2) and Markov Random Field (MRF) models (Run 3). The conventional Query Likelihood model was implemented as the baseline (Run 1).

Wani, S., Muthusamy, V. R., Shaheen, N. J., Yadlapati, R., Wilson, R., Abrams, J. A., . . . Komanduri, S. (2017). **Development of quality indicators for endoscopic eradication therapies in Barrett's esophagus: the TREAT-BE (Treatment with Resection and Endoscopic Ablation Techniques for Barrett's Esophagus) Consortium.** *Gastrointestinal Endoscopy*, 86(1), 1-17.e13. doi:10.1016/j.gie.2017.03.010

Wani, S., Muthusamy, V. R., Shaheen, N. J., Yadlapati, R., Wilson, R., Abrams, J. A., . . . Komanduri, S. (2017). **Development of Quality Indicators for Endoscopic Eradication Therapies in Barrett's Esophagus: The TREAT-BE (Treatment With Resection and Endoscopic Ablation Techniques for Barrett's Esophagus) Consortium.** *Am J Gastroenterol*. doi:10.1038/ajg.2017.166

Am J Gastroenterol advance online publication, 1 June 2017; doi:10.1038/ajg.2017.166.

Weaver, K. E., Chen, Y., Miiller, E. M., Johnson, J. N., Dangler, A. A., Manias, D. A., . . . Dunny, G. M. (2017). **Examination of Enterococcus faecalis toxin-antitoxin system toxin Fst function utilizing a pheromone-inducible expression vector with tight repression and broad dynamic range.** *Journal of Bacteriology*, 199(12). doi:10.1128/JB.00065-17

Tools for regulated gene expression in *Enterococcus faecalis* are extremely limited. In this report, we describe the construction of an expression vector for *E. faecalis*, designated pCIE, utilizing the PQ pheromone-responsive promoter of plasmid pCF10. We demonstrate that this promoter is tightly repressed, responds to nanogram quantities of the peptide pheromone, and has a large dynamic range. To demonstrate its utility, the promoter was used to control expression of the toxic peptides of two par family toxin-antitoxin (TA) loci present in *E. faecalis*, parAD1 of the pAD1 plasmid and parEF0409 located on the *E. faecalis* chromosome. The results demonstrated differences in the modes of regulation of toxin expression and in the effects of toxins of these two related systems. We anticipate that this vector will be useful for further investigation of

par TA system function as well as the regulated expression of other genes in *E. faecalis*. © 2017 American Society for Microbiology. All Rights Reserved.

Webb, B. C., Whittle, T., & Schwarz, E. (2015). **Provision of dental care in aged care facilities NSW Australia- Part 2 as perceived by the carers (care providers)**. *Gerodontology*, 32(4), 254-259. doi:10.1111/ger.12103

OBJECTIVES: To investigate carers' perception of the provision of dental care in aged care facilities (ACFs) New South Wales (NSW), Australia. **BACKGROUND:** Carers are responsible for 'hands-on, day-to-day' care of residents, including dental care, yet there were no specific figures available concerning their role in NSW ACFs. **MATERIALS AND METHODS:** Questionnaires were mailed to 406 NSW directors of nursing (DONs) requesting completion by a carer who was proficient in English and without the influence of the DON. The 23-item questionnaire was presented in 4 sections, and the data qualitatively analysed. **RESULTS:** 211 questionnaires were completed and returned, giving a response rate of 52%. Carers were mostly female (91.9%) in the 40-50 and >50 age groups. Oral health training had been received by 66.7% of carers, and although 73.2% thought that their training was adequate, carers in general requested further training. Long waiting periods for government dental services (69.4%) and resident unable to communicate oral health problems (69.2%) were seen as the most frequent barriers to dental care. Almost all carers reported the availability of electric tooth brushes, fluoride gel, disclosing tablets/gel, interdental brushes and the use of a foam mouth prop, while few reported the use of other dental care products. **CONCLUSION:** As carers provided almost all of oral health care for residents, emphasis should be placed on training in geriatric dental care techniques and use of dental products.

Weine, S. M., Stone, A., Saeed, A., Shanfield, S., Beahrs, J., Gutman, A., & Mihajlovic, A. (2017). **Violent Extremism, Community-Based Violence Prevention, and Mental Health Professionals**. *Journal of Nervous and Mental Disease*, 205(1), 54-57. doi:10.1097/nmd.0000000000000634

New community-based initiatives being developed to address violent extremism in the United States are utilizing mental health services and leadership. This article reviews current approaches to preventing violent extremism, the contribution that mental illness and psychosocial problems can make to violent extremism, and the rationale for integrating mental health strategies into preventing violent extremism. The authors describe a community-based targeted violence prevention model and the potential roles of mental health professionals. This model consists of a multidisciplinary team that assesses at-risk individuals with comprehensive threat and behavioral evaluations, arranges for ongoing support and treatment, conducts follow-up evaluations, and offers outreach, education, and resources for communities. This model would enable mental health professionals in local communities to play key roles in preventing violent extremism through their practice and leadership.

Weiss, J. B., Weber, S., Marzulla, T., & Raber, J. (2017). **Pharmacological inhibition of Anaplastic Lymphoma Kinase rescues spatial memory impairments in Neurofibromatosis 1 mutant mice**. *Behav Brain Res*, 332, 337-342. doi:10.1016/j.bbr.2017.06.024

Heterozygous Neurofibromatosis 1 (NF1) loss of function mutations are found in 90% of patients with neurofibromatosis, a syndrome associated with disabling cognitive impairment. *Drosophila* studies have demonstrated a genetic interaction between Anaplastic Lymphoma Kinase (Alk) and NF1 in cognitive performance. In addition, pharmacologic inhibition of Alk improves cognitive performance in heterozygous NF1 mutant flies. In this study, we tested whether pharmacological inhibition of Alk in heterozygous NF1 mutant mice attenuates or rescues cognitive impairments. Cognitive impairment of spatial memory retention observed in heterozygous NF1 mutant mice was rescued by the Alk inhibitor. These data support the hypothesis that inhibition of Alk may cognitively benefit patients with Neurofibromatosis 1.

Wieck, M. M., Hamilton, N. A., & Krishnaswami, S. (2016). **A cost and outcome analysis of pediatric single-incision appendectomy.** *Journal of Surgical Research*, 203(2), 253-257. doi:10.1016/j.jss.2016.04.033

BACKGROUND: For appendicitis, single-incision laparoscopic appendectomy (SIA) has been proposed as an alternative to 3-port appendectomy (3PA). However, there remains controversy regarding outcomes and cost of SIA. We sought to review our experience with these two techniques to identify differences in these factors. **MATERIALS AND METHODS:** The charts of children (0-17 y) who underwent appendectomy at a tertiary pediatric hospital from 2011-2014 were retrospectively reviewed. Appendectomy was either performed through traditional 3PA or SIA (laparoscopically assisted via externalization through an umbilical incision). Demographic data including age, body mass index, comorbidities, and gender were examined. Information on perforation, operative time and cost, length of stay, and infectious complications for both SIA and 3PA was identified. Data were analyzed using student t tests and chi square analysis. **RESULTS:** A total of 337 patients underwent appendectomy (141 SIA and 197 3PA), 35.6% of whom (40 SIA, 80 3PA) had perforated appendicitis. For nonperforated appendicitis, SIA had significantly shorter operative times, decreased operative costs, and length of stay. However, these differences were not found for perforated appendicitis. Regardless of appendicitis severity, there was no difference in rates of wound infection, abscess, or readmission between the two techniques. **CONCLUSIONS:** Our study suggests that SIA is a faster, more cost effective alternative than 3PA for acute appendicitis. SIA did not result in increased infection rates for acute or perforated appendicitis and can be considered an equivalent alternative to 3PA in the surgical management of appendicitis.

Wilkin, J., Rosenfeld, L., Allen, A., Baltas, R., Baptista, A., He, R., . . . Smith, J. (2017). **Advancing coastal ocean modelling, analysis, and prediction for the US Integrated Ocean Observing System.** *Journal of Operational Oceanography*, 1-12. doi:10.1080/1755876X.2017.1322026

This paper outlines strategies that would advance coastal ocean modelling, analysis and prediction as a complement to the observing and data management activities of the coastal components of the US Integrated Ocean Observing System (IOOS®) and the Global Ocean Observing System (GOOS). The views presented are the consensus of a group of US-based researchers with a cross-section of coastal oceanography and ocean modelling expertise and community representation drawn from Regional and US Federal partners in IOOS. Priorities for research and development are suggested that would enhance the value of IOOS observations through model-based synthesis, deliver better model-based information products, and assist the design, evaluation, and operation of the observing system itself. The proposed priorities are: model coupling, data assimilation, nearshore processes, cyberinfrastructure and model skill assessment, modelling for observing system design, evaluation and operation, ensemble prediction, and fast predictors. Approaches are suggested to accomplish substantial progress in a 3–8-year timeframe. In addition, the group proposes steps to promote collaboration between research and operations groups in Regional Associations, US Federal Agencies, and the international ocean research community in general that would foster coordination on scientific and technical issues, and strengthen federal–academic partnerships benefiting IOOS stakeholders and end users. © 2017 Institute of Marine Engineering, Science & Technology

Wolsk, E., Claggett, B., Pfeffer, M. A., Diaz, R., Dickstein, K., Gerstein, H. C., . . . Kober, L. (2017). **Role of B-Type Natriuretic Peptide and N-Terminal Prohormone BNP as Predictors of Cardiovascular Morbidity and Mortality in Patients With a Recent Coronary Event and Type 2 Diabetes Mellitus.** *J Am Heart Assoc*, 6(6). doi:10.1161/jaha.116.004743

BACKGROUND: Natriuretic peptides are recognized as important predictors of cardiovascular events in patients with heart failure, but less is known about their prognostic importance in patients with acute coronary syndrome. We sought to determine whether B-type natriuretic peptide (BNP) and N-terminal prohormone B-type natriuretic peptide (NT-proBNP) could enhance risk prediction of a broad range of cardiovascular outcomes in patients with acute coronary syndrome and type 2 diabetes mellitus. **METHODS AND RESULTS:** Patients with a recent acute coronary syndrome and type 2 diabetes mellitus were prospectively enrolled in the ELIXA

trial (n=5525, follow-up time 26 months). Best risk models were constructed from relevant baseline variables with and without BNP/NT-proBNP. C statistics, Net Reclassification Index, and Integrated Discrimination Index were analyzed to estimate the value of adding BNP or NT-proBNP to best risk models. Overall, BNP and NT-proBNP were the most important predictors of all outcomes examined, irrespective of history of heart failure or any prior cardiovascular disease. BNP significantly improved C statistics when added to risk models for each outcome examined, the strongest increments being in death (0.77-0.82, $P < 0.001$), cardiovascular death (0.77-0.83, $P < 0.001$), and heart failure (0.84-0.87, $P < 0.001$). BNP or NT-proBNP alone predicted death as well as all other variables combined (0.77 versus 0.77). CONCLUSIONS: In patients with a recent acute coronary syndrome and type 2 diabetes mellitus, BNP and NT-proBNP were powerful predictors of cardiovascular outcomes beyond heart failure and death, ie, were also predictive of MI and stroke. Natriuretic peptides added as much predictive information about death as all other conventional variables combined. CLINICAL TRIAL REGISTRATION: URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT01147250.

Woodward, Z., Williams, J. L., & Sonnenberg, A. (2016). **Length of endoscopic workup in gastrointestinal bleeding.** *Eur J Gastroenterol Hepatol*, 28(10), 1166-1171. doi:10.1097/meg.0000000000000693

BACKGROUND: The number of procedures utilized in the general management of gastrointestinal bleeding (GIB) has not been investigated previously. We used the National Endoscopic Database of the Clinical Outcomes Research Initiative for an observational study to analyze the average length of workup in GIB. METHODS: The electronic database was queried for all patients aged 18 years and older who underwent an endoscopic evaluation for any bleeding indication between 2000 and 2014. Data were stratified by indication, type, and number of endoscopies per patient, and length of workup. RESULTS: A total of 603 807 endoscopic procedures among 451 470 individual patients were used in the workup of GIB, with 152 337 procedures among 113 030 patients (25%) being performed as a secondary procedure. The average length was 2.4+/-0.9 procedures per workup in procedural sequences involving multiple endoscopies. The length of workup was independent of the initial type of GIB. An esophago-gastro-duodenoscopy (EGD), followed by a colonoscopy or a colonoscopy, followed by an EGD were the most frequent combinations. In another substantial fraction of two consecutive procedures, the first and the second procedure were identical. This pattern applied not only to EGD and colonoscopy but also to flexible sigmoidoscopy, enteroscopy, and video capsule endoscopy. CONCLUSION: The majority of patients with GIB require only one type of endoscopy to manage their bleeding. However, in a quarter of patients, on average, 2.4 procedures are needed. Previous trials assessing the outcomes of individual types of endoscopy may have exaggerated their overall success rates in diagnosing and treating GIB.

Worth, P. J., Kaur, T., Diggs, B. S., Sheppard, B. C., Hunter, J. G., & Dolan, J. P. (2016). **Major bile duct injury requiring operative reconstruction after laparoscopic cholecystectomy: a follow-on study.** *Surgical Endoscopy*, 30(5), 1839-1846. doi:10.1007/s00464-015-4469-2

BACKGROUND: Bile duct injury (BDI) after laparoscopic cholecystectomy (LC) has significant cost impact and is a significant source of morbidity and mortality. We undertook a population-based assessment of the national experience with BDI between 2001 and 2011 and compared this to our report for the prior decade. METHODS: Using the nationwide inpatient sample (NIS) for 2001-2011, we identified patients who underwent LC or partial cholecystectomy, with and without biliary reconstruction. Data were analyzed using methods that accounted for the hierarchical, stratified random sampling of the NIS. Both univariate modeling and multivariate modeling were performed. RESULTS: LCs increased from 71.1 % in 2001 to 79.0 % in 2011 ($p < 0.0001$). Annual mortality decreased from 0.56 to 0.38 % ($p = 0.002$). In 2001, 0.11 % of LCs were associated with biliary reconstruction versus 0.09 % in 2011 ($p = 0.15$) with rates ranging from 0.08 to 0.12 %. The need for reconstruction was associated with an average in-hospital mortality rate of 4.4 %. Mortality rates from LC remained consistent across the study period (average mortality, 0.10 %, $p = 0.57$). Under multivariate analysis, admission to rural or urban non-teaching centers was associated with a decreased rate of injury; the majority of major BDIs were admitted from clinic or outpatient settings. These results are

consistent with results from the prior decade. Neither emergent admission nor race was associated with increased odds of BDI, and this differs from our prior analysis. CONCLUSION: LC continued to increase in utilization between 2001 and 2011. Although rates of BDI have decreased, the need for reconstruction continues to be associated with a significant mortality. In addition, mortality related to biliary reconstruction is also higher than previously published series and may reflect the complexity of managing biliary injury as well as the higher likelihood of these patients having comorbid conditions.

Wozniczka, J., Canepa, C., Mirarchi, A., & Solomon, J. S. (2017). **Complications Following Collagenase Treatment for Dupuytren Contracture.** *Hand (N Y)*, 1558944717711461. doi:10.1177/1558944717711461

BACKGROUND: Collagenase Clostridium histolyticum (CCH) injection and manipulation is a relatively new method for treating Dupuytren contracture that is growing in popularity. Although side effects such as swelling and ecchymosis are common, they are typically mild and self-limited. Major complications are rare but have included flexor tendon rupture and complex regional pain syndrome. METHODS: This study describes a case report of 2 patients seen at our institution. RESULTS: Here, we report 2 patients seen at our institution each with different, yet serious complications after CCH injection and manipulation. One patient had extensive skin loss and chose amputation over reconstruction. The other patient had loss of perfusion and required finger amputation. CONCLUSIONS: Although it is unclear how directly the administration of CCH is connected to the observed complications, physicians should recognize the potential for serious rare complications in any treatment of Dupuytren contracture.

Yang, S. J., Salek, S., & Rosenbaum, J. T. (2017). **Ocular sarcoidosis: new diagnostic modalities and treatment.** *Current Opinion in Pulmonary Medicine*. doi:10.1097/mcp.0000000000000409

PURPOSE OF REVIEW: Ocular involvement in sarcoidosis is present in up to 80% of patients and is frequently manifested before diagnosis of the underlying systemic disease. Considering the therapeutic consequences, early diagnosis of the underlying disease is advantageous in patients presenting with ocular inflammation. There are several ocular findings suggestive of underlying sarcoidosis, such as granulomatous keratic precipitates, iris nodules, cells in the vitreous humor known as snowballs and snowbanks, and retinal periphlebitis. High suspicion is crucial for the diagnosis of sarcoidosis. This review on ocular sarcoidosis will mainly focus on new diagnostic and treatment modalities. RECENT FINDINGS: Recent studies found possible new diagnostic indicators for the diagnosis of ocular sarcoidosis which include not only serum profiles but also vitreous sample analysis. Ophthalmologic imaging techniques have improved to investigate the ocular structure in detail. Results from recent uveitis clinical trials have included sarcoidosis as an underlying cause and have reported positive results. SUMMARY: The diagnosis of ocular sarcoidosis can be challenging in some cases. High suspicion is important to diagnose ocular sarcoidosis with various laboratory and ophthalmic tools. There are many possible options for the treatment of ocular sarcoidosis including various biologic agents.

Yee, L. M., Sandoval, G., Bailit, J., Reddy, U. M., Wapner, R. J., Varner, M. W., . . . Tolosa, J. E. (2016). **Maternal and Neonatal Outcomes With Early Compared With Delayed Pushing Among Nulliparous Women.** *Obstet Gynecol*, 128(5), 1039-1047. doi:10.1097/aog.0000000000001683

OBJECTIVE: To describe factors associated with delayed pushing and evaluate the relationship between delayed pushing and perinatal outcomes in nulliparous women with singleton term gestations. METHODS: This was a secondary analysis of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Assessment of Perinatal Excellence cohort of 115,502 women and their neonates born in 25 U.S. hospitals from 2008 to 2011. Nulliparous women with singleton, cephalic, nonanomalous term births who achieved 10-cm cervical dilation were included. Women in whom pushing was delayed by 60 minutes or greater (delayed group) were compared with those who initiated pushing within 30 minutes (early group). Multivariable regression analyses were used to assess the independent association of delayed pushing with

mode of delivery, length of the second stage, and other maternal and perinatal outcomes (significance defined as $P < .05$). RESULTS: Of 21,034 women in the primary analysis sample, pushing was delayed in 18.4% ($n=3,870$). Women who were older, privately insured, or non-Hispanic white as well as those who had induction or augmentation of labor, diabetes, or epidural analgesia were more likely to have delayed pushing. Delayed pushing was more common when the second stage began during daytime hours or in hospitals with dedicated 24-hour obstetric anesthesia, although differences were small. After adjusting for differences in baseline and labor characteristics including center, women in the delayed group had longer mean durations of the second stage (191 compared with 84 minutes, $P < .001$) and of active pushing (86 compared with 76 minutes, $P < .001$). Delayed pushing was associated with greater rates of cesarean delivery (11.2% compared with 5.1%; adjusted odds ratio [OR] 1.86, 95% confidence interval [CI] 1.63-2.12), operative vaginal delivery (adjusted OR 1.26, 95% CI 1.14-1.40), postpartum hemorrhage (adjusted OR 1.43, 95% CI 1.05-1.95), and blood transfusion (adjusted OR 1.51, 95% CI 1.04-2.17). Delayed pushing was not associated with increased odds of adverse neonatal outcomes compared with early pushing. CONCLUSION: In this large birth cohort, delayed pushing was associated with longer second stage duration, increased odds of cesarean delivery, and increased odds of postpartum hemorrhage, but was not associated with neonatal morbidity.

Yieh, L., & Warren, J. B. (2017). **Does umbilical cord milking result in higher measures of systemic blood flow in preterm infants?** *Acta Paediatrica*. doi:10.1111/apa.13926

Yonge, J. D., & Schreiber, M. A. (2016). **The pragmatic randomized optimal platelet and plasma ratios trial: what does it mean for remote damage control resuscitation?** *Transfusion*, 56 Suppl 2, S149-156. doi:10.1111/trf.13502

BACKGROUND: Implications from the pragmatic, randomize, optimal platelet and plasma ratios (PROPPR) trial are critical for remote damage control resuscitation (DCR). Utilizing DCR principals in remote settings can combat early mortality from hemorrhage. Identifying the appropriate transfusion strategy is mandatory prior to adopting prehospital hemostatic resuscitation strategies. STUDY DESIGN AND METHODS: The PROPPR study was examined in relation to the following questions: 1) Why is it important to have blood products in the prehospital setting?; 2) Which products should be investigated for prehospital hemostatic resuscitation?; 3) What is the appropriate ratio of blood product transfusion?; and 4) What are the appropriate indications for hemostatic resuscitation? RESULTS: PROPPR demonstrates that early and balanced blood product transfusion ratios reduced mortality in all patients at 3 hours and death from exsanguination at 24 hours ($p = 0.03$). The median time to death from exsanguination was 2.3 hours, highlighting the need for point-of-injury DCR capabilities. A 1:1:1 transfusion ratio of plasma:platelets:packed red blood cells increased the percentage of patients achieving anatomic hemostasis ($p = 0.006$). PROPPR used the assessment of blood consumption score to identify patients likely to require ongoing hemostatic resuscitation. The critical administration threshold predicted patient mortality and identified patients likely to require ongoing hemostatic resuscitation. CONCLUSION: A balanced resuscitation strategy demonstrates an early survival benefit, decreased death from exsanguination at 24 hours and a greater likelihood of achieving hemostasis in critically injured patients receiving a 1:1:1 ratio of plasma:platelets:PRBCs. This finding highlights the need to import DCR principals to remote locations.

Yoshida, H., Imura, H., Goto, T., Nakamata, T., Daya, M. R., & Kamiya, T. (2017). **Acute Carpal Tunnel Syndrome Due to Pyogenic Flexor Tenosynovitis without Any Antecedent Injury.** *Internal Medicine*, 56(11), 1439-1442. doi:10.2169/internalmedicine.56.7584

We herein report a case of acute carpal tunnel syndrome due to pyogenic flexor tenosynovitis in the absence of any antecedent injury whose rapid progression and course was similar to that seen with necrotizing fasciitis. This potentially disastrous clinical condition must be promptly recognized, since it needs early surgical management to prevent morbidity.

Young, R. A., Casey, D., Singer, D., Waller, E., & Carney, P. A. (2017). **Early career outcomes of family medicine residency graduates exposed to innovative flexible longitudinal tracks.** *Family Medicine, 49*(5), 353-360.

BACKGROUND AND OBJECTIVES: The Preparing the Personal Physician for Practice (P4) project used a case series design to study innovations in the content, length, structure, and location of residency training in 14 geographically diverse family medicine programs between 2007 and 2012. We aimed to explore how offering flexible longitudinal tracks (FLT) affected graduates' scope of practice, particularly in maternal child health (MCH), which included at least 17 months of focused training that increased each year over 4 years. **METHODS:** We administered a cross-sectional survey to graduates of P4 residencies approximately 18 months after they completed training (2011–2014) and compared graduates of the John Peter Smith (JPS) Family Medicine Residency MCH FLT to all other P4 graduates. **RESULTS:** The overall response rate was 81.8% (365/446). JPS graduates who completed the flexible MCH track (n=15) compared to all other P4 graduates (n=332) were more likely to deliver babies (13/15, 86.7% versus 48/324, 14.6%) and perform C-sections as the primary surgeon (12/15, 80.0% versus 15/322, 4.7%). Additional areas of expanded scope associated with the MCH track included endoscopy (4/15, 26.7% versus 10/323, 3.1%), the care of hospitalized adults and associated procedures (central lines, eg: 8/15, 53.3% versus 47/322, 14.6%), and the care of hospitalized children (13/15, 86.7% versus 111/323, 34.4%). **CONCLUSIONS:** Graduating from the JPS MCH FLT was associated with a higher provision of maternal, child, and ill adult patient care services, including associated procedures. © 2017, Society of Teachers of Family Medicine. All rights reserved.

Zaccari, B., Layne, W., Loftis, J., & Penn, P. (2017). **The Participant's Voice: A Mixed-Method Evaluation of a Mixed-Gender Seeking Safety Group.** *Alcoholism Treatment Quarterly, 1-19.* doi:10.1080/07347324.2017.1322416

This study used mixed methods to evaluate Seeking Safety (a cognitive-behavioral based therapy for co-occurring mental health and substance use disorders) with a mixed-gender group. The authors analyzed posttraumatic stress disorder (PTSD) symptom change and feedback among clients of a recovery facility in Arizona (N = 156). Pre-post and correlational analyses were performed. Attendance was associated with reductions in PTSD symptoms ($t = 2.56, p = .006$; $F = 2.86, p = .06$) with no difference for gender. A strong positive correlation was found between ratings of session helpfulness and likeliness to use session skills ($r = .90, p < .001$). Qualitative data analyzed for module themes are also discussed. © 2017, Taylor & Francis. All rights reserved.

Zhang, D., Wu, B., Wang, P., Wang, Y., Lu, P., Nechiporuk, T., . . . Zhou, B. (2016). **Non-CpG methylation by DNMT3B facilitates REST binding and gene silencing in developing mouse hearts.** *Nucleic Acids Research, 45*(6), 3102-3115. doi:10.1093/nar/gkw1258

The dynamic interaction of DNA methylation and transcription factor binding in regulating spatiotemporal gene expression is essential for embryogenesis, but the underlying mechanisms remain understudied. In this study, using mouse models and integration of in vitro and in vivo genetic and epigenetic analyses, we show that the binding of REST (repressor element 1 (RE1) silencing transcription factor; also known as NRSF) to its cognate RE1 sequences is temporally regulated by non-CpG methylation. This process is dependent on DNA methyltransferase 3B (DNMT3B) and leads to suppression of adult cardiac genes in developing hearts. We demonstrate that DNMT3B preferentially mediates non-CpG methylation of REST-targeted genes in the developing heart. Downregulation of DNMT3B results in decreased non-CpG methylation of RE1 sequences, reduced REST occupancy, and consequently release of the transcription suppression during later cardiac development. Together, these findings reveal a critical gene silencing mechanism in developing mammalian hearts that is regulated by the dynamic interaction of DNMT3B-mediated non-CpG methylation and REST binding. © The Author(s) 2016.

Zhang, J., Liu, D., Li, G., Staveley-O'Carroll, K. F., Graff, J. N., Li, Z., & Wu, J. D. (2017). **Antibody-mediated neutralization of soluble MIC significantly enhances CTLA4 blockade therapy.** *Sci Adv*, 3(5), e1602133. doi:10.1126/sciadv.1602133

Antibody therapy targeting cytotoxic T lymphocyte-associated antigen 4 (CTLA4) elicited survival benefits in cancer patients; however, the overall response rate is limited. In addition, anti-CTLA4 antibody therapy induces a high rate of immune-related adverse events. The underlying factors that may influence anti-CTLA4 antibody therapy are not well defined. We report the impact of a cancer-derived immune modulator, the human-soluble natural killer group 2D (NKG2D) ligand sMIC (soluble major histocompatibility complex I chain-related molecule), on the therapeutic outcome of anti-CTLA4 antibody using an MIC transgenic spontaneous TRAMP (transgenic adenocarcinoma of the mouse prostate)/MIC tumor model. Unexpectedly, animals with elevated serum sMIC (sMIChi) responded poorly to anti-CTLA4 antibody therapy, with significantly shortened survival due to increased lung metastasis. These sMIChi animals also developed colitis in response to anti-CTLA4 antibody therapy. Coadministration of an sMIC-neutralizing monoclonal antibody with the anti-CTLA4 antibody alleviated treatment-induced colitis in sMIChi animals and generated a cooperative antitumor therapeutic effect by synergistically augmenting innate and adoptive antitumor immune responses. Our findings imply that a new combination therapy could improve the clinical response to anti-CTLA4 antibody therapy. Our findings also suggest that prescreening cancer patients for serum sMIC may help in selecting candidates who will elicit a better response to anti-CTLA4 antibody therapy.

Zhang, Y., Huang, T., Jorgens, D. M., Nickerson, A., Lin, L. J., Pelz, J., . . . Nan, X. (2017). **Quantitating morphological changes in biological samples during scanning electron microscopy sample preparation with correlative super-resolution microscopy.** *PLoS ONE*, 12(5), e0176839. doi:10.1371/journal.pone.0176839

Sample preparation is critical to biological electron microscopy (EM), and there have been continuous efforts on optimizing the procedures to best preserve structures of interest in the sample. However, a quantitative characterization of the morphological changes associated with each step in EM sample preparation is currently lacking. Using correlative EM and superresolution microscopy (SRM), we have examined the effects of different drying methods as well as osmium tetroxide (OsO₄) post-fixation on cell morphology during scanning electron microscopy (SEM) sample preparation. Here, SRM images of the sample acquired under hydrated conditions were used as a baseline for evaluating morphological changes as the sample went through SEM sample processing. We found that both chemical drying and critical point drying lead to a mild cellular boundary retraction of ~60 nm. Post-fixation by OsO₄ causes at least 40 nm additional boundary retraction. We also found that coating coverslips with adhesion molecules such as fibronectin prior to cell plating helps reduce cell distortion from OsO₄ post-fixation. These quantitative measurements offer useful information for identifying causes of cell distortions in SEM sample preparation and improving current procedures.

Zuckerman, D. M., & Chong, L. T. (2017) Weighted Ensemble Simulation: Review of Methodology, Applications, and Software. *Vol. 46. Annual Review of Biophysics* (pp. 43-57): Annual Reviews Inc.

The weighted ensemble (WE) methodology orchestrates quasi-independent parallel simulations run with intermittent communication that can enhance sampling of rare events such as protein conformational changes, folding, and binding. The WE strategy can achieve superlinear scaling—the unbiased estimation of key observables such as rate constants and equilibrium state populations to greater precision than would be possible with ordinary parallel simulation. WE software can be used to control any dynamics engine, such as standard molecular dynamics and cell-modeling packages. This article reviews the theoretical basis of WE and goes on to describe successful applications to a number of complex biological processes—protein conformational transitions, (un)binding, and assembly processes, as well as cell-scale processes in systems biology. We furthermore discuss the challenges that need to be overcome in the next phase of WE methodological development. Overall, the combined advances in WE methodology and software have enabled the

simulation of long-timescale processes that would otherwise not be practical on typical computing resources using standard simulation. © 2017 by Annual Reviews. All rights reserved.